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### EXPERIENCE WITH SURGICAL AND RADIATION THERAPY IN CARCINOMA OF THE CORPUS UTERI*

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TWO HUNDRED AND EIGHTY-THREE patients with carcinoma of the corpus uteri were admitted to the Gynecological Service at the Memorial Hospital during the fifteen-year period from 1918 to 1932. Eighty-six of these cases had residual or recurrent carcinoma after treatment by surgery or radiation elsewhere and are not included in the following review. One hundred and ninety-seven received their primary treatment at the Memorial Hospital, and it is these cases which constitute the subject material for this paper. All but five patients were followed for five years or more or until death. In the statistics which follow, the five patients lost track of are counted as deaths from carcinoma, as are the cases in which the cause of death is not definitely known.

Of this group of 197 patients 93 were treated by a combination of surgery and radiation, 96 received radiation therapy alone, and 8 were treated by surgery alone. All cases were proved histologically to be carcinoma of the corpus uteri. The cases have been classified both clinically and histologically, and these classifications have been correlated with end results as have the various techniques of treatment which were employed.

The *age* of the patients in this series ranged from 19 to 79. The average age was 58 and the ten-year period of greatest incidence was from 55 to 64. Table I shows how the cases were distributed.

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NOTE: The Editor accepts no responsibility for the views and statements of authors as published in their ''Original Communications.''

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TABLE I.  AGE

| | | | | |
|---|---|---|---|---|
| Youngest | 19 | | Oldest | 79 |
| | Average age | 58 | | |
| 10-year period of greatest incidence | | | | 55-64 |
| 19-40 | 3% | | 55-59 | 25% |
| 40-44 | 3% | | 60-64 | 20% |
| 45-49 | 12% | | 65-69 | 14% |
| 50-54 | 16% | | 70-74 | 5% |
| | | 75-79 | 2% | |

Consideration of *marital status* revealed that 83 per cent were married or widowed, 16 per cent single and that in 1 per cent marital status was not stated in the patient's record.  Fifty-four per cent of the patients had one or more pregnancies, 36 per cent had never been pregnant, and in 10 per cent information in regard to this point was lacking.  It is of interest to mention in this connection that not over 10 per cent of reported cases of patients with carcinoma of the cervix are nulliparous.

The *incidence of previous pelvic operations* was low (12 per cent).  Eighty-eight per cent of the patients had no previous pelvic surgery, suggesting at least that the pelvic organs up to the time of the development of carcinoma had not been grossly abnormal.

TABLE II.  INCIDENCE OF PREVIOUS PELVIC OPERATIONS

| | PER CENT |
|---|---|
| Oophorectomy | 4 |
| Dilatation and curettage | 2 |
| Cauterization of cervix | 2 |
| Perineal repair | 2 |
| Suspension of uterus | 1 |
| Myomectomy | 1 |
| *No previous pelvic operation* | 88 |

The *symptoms* of carcinoma of the corpus uteri begin, as a rule, after the menopause.  In this series 78 per cent of the patients stated that the onset of symptoms occurred after menstruation had ceased.  The average age at menopause was 50 years. The duration of symptoms varied from less than a month to over three years. Thirty-seven of the patients waited longer than a year before seeking medical attention.

The most important and most frequent symptom of carcinoma of the corpus uteri is *uterine bleeding*.  It was present in 98 per cent of the entire group of 197 cases. In 97 per cent the bleeding was postmenopausal or intermenstrual, in 1 per cent menorrhagia only was noted.  Uterine bleeding was usually slight and intermittent at first, tending to become more constant and profuse as time went on.

*Pain,* for the most part localized in the pelvis and lower abdomen, was present in 27 per cent of the cases and is a symptom of some prognostic significance.  Of the 53 patients complaining of pain, 66 per cent later died of carcinoma, whereas of the 144 patients without pain only 37 per cent died of carcinoma.  It is also of interest that 43 per cent of the patients complaining of pain when their history was taken and who later died of carcinoma had no palpable evidence of extension beyond the uterus at initial examination.  This suggests that pain in some cases at least indicates extension of carcinoma beyond the uterus before such extension can be verified by clinical examination.

*Discharge,* usually watery and malodorous, was present in at least 35 per cent of the cases, but it was not a prominent symptom in the patients' minds and consequently its presence or absence was not always recorded.  It occasionally occurred before the onset of uterine bleeding, but it was in almost every case the bleeding which caused the patient to seek medical advice.

TABLE III. SYMPTOMS

| | | |
|---|---|---|
| Uterine bleeding | | 98% |
| Postmenopausal or intermenstrual | 97% | |
| Menorrhagia only | 1% | |
| No bleeding | 1% | |
| Not stated | 1% | |
| Pain (pelvis, lower abdomen, back) | | 27% |
| Discharge | | 35% |
| Tumor | | 1% |

TABLE IV. PAIN AS A PROGNOSTIC FACTOR

| | | |
|---|---|---|
| Number of patients with pain | | 53 |
| Died of carcinoma | 35 or 66% | |
| Number of patients without pain | | 144 |
| Died of carcinoma | 53 or 37% | |

Information in regard to the *association* of carcinoma of the corpus *with fibromyoma* was gained from a review of the 101 cases which were subjected to abdominal operation. Thirty-eight per cent of these were found to have both fibromyoma and carcinoma of the body of the uterus. This serves to emphasize the fact that the source of uterine bleeding cannot be considered as nonmalignant just because fibroids are palpable. An examination of endometrial tissue is a prerequisite to an accurate diagnosis.

The entire series of 197 cases was divided into clinical groups according to the extent of the carcinoma as evidenced by observation and palpation. Into Group I were placed those patients in whom there was no palpable enlargement of the uterus. Group II was made up of patients in whom the uterus was enlarged but was not over the size of a two and one-half months' gestation. Approximately half of all of the cases fell into this group. This size (two and one-half months' gestation) was not decided on arbitrarily but was arrived at by first determining the survival rates for several different degrees of enlargement. A sharp drop in five-year survivals was found when the uterus was the size of a three, four, or five months' gestation. The point at which the prognosis seemed to become definitely less favorable was when the uterus reached the size of a three months' gestation. Group IIA was reserved for patients in whom the uterus was larger than a two and one-half months' gestation, but in which the disease was still confined to the uterus so far as could be determined clinically. In Group III were placed all cases in which there was evidence of extension beyond the uterus at the time of first examination. Table V indicates the number and percentage of cases in each clinical group.

TABLE V. CARCINOMA OF CORPUS UTERI. CLINICAL GROUPS

| | CLINICAL GROUP | NUMBER OF CASES | PERCENTAGE |
|---|---|---|---|
| I. | Uterus not enlarged | 42 | 22 |
| II. | Uterus enlarged but not over size of 2½ mo. gestation | 97 | 49 |
| IIA. | Uterus larger than 2½ mo. gestation | 20 | 10 |
| III. | Extension of carcinoma beyond uterus | 38 | 19 |

The next step was to determine the *relation of the clinical groups to prognosis* as evidenced by five-year survivals. It was found that when the uterus was not larger than a two and one-half months' gestation and when there was no clinical evidence of extension of carcinoma beyond the uterus the five-year survival rate was 60 per cent. When the uterus was larger than a two and one-half months' gestation, the five-year survivals were only 35 per cent, and when there was extension of carcinoma beyond the uterus, only 10 per cent of the patients lived five years. These figures are based on clinical group only and are without regard to method of treatment employed. However, it will be seen from consulting Table VII that they roughly parallel those for patients treated by radiation alone and by radiation combined with surgery.

Ninety-six patients were treated by radiation alone and 93 by a combination of radiation and surgery. Only 8 patients were treated by surgery alone, and it is felt that this is too small a group to be of value for comparison of end results with the results of the other methods of treatment. The other two groups, however, are nearly equal and are of sufficient size so that statistics based upon them may be considered as representative of the two types of treatment. It should be stated that decision as to whether treatment should be by radiation followed by complete abdominal hysterectomy or by radiation alone was influenced greatly by the age and general condition of the patient. Those patients treated by radiation alone were for the most part either poor surgical risks due to advanced age, obesity, or intercurrent disease, or were individuals who refused operation. The authors believe that whenever possible intrauterine radiation should be followed by complete abdominal hysterectomy. Statistics to show the reasons for this opinion will be presented presently.

TABLE VI.  CARCINOMA OF CORPUS UTERI.  RELATION OF CLINICAL GROUP TO PROGNOSIS*

| CLINICAL GROUP | NUMBER OF CASES | 5-YEAR SURVIVAL PER CENT | DEATH FROM CARCINOMA IN LESS THAN 1 YEAR PER CENT |
|---|---|---|---|
| I.   Uterus not enlarged | 42 | 62 | 12 |
| II.   Uterus enlarged but not over size of 2½ mo. gestation | 97 | 59 | 5 |
| IIA. Uterus larger than 2½ mo. gestation | 20 | 35 | 25 |
| III.  Extension of carcinoma beyond uterus | 38 | 10 | 66 |
| Total | 197 | | |

*Without regard to method of treatment employed.

TABLE VII.  CARCINOMA OF CORPUS UTERI.  RELATION OF CLINICAL GROUP TO END RESULTS UNDER RADIATION ALONE AND RADIATION COMBINED WITH SURGERY

| CLINICAL GROUP | RADIATION ALONE | | RADIATION AND SURGERY | |
|---|---|---|---|---|
| | NO. OF CASES | 5-YEAR SURVIVAL PER CENT | NO. OF CASES | 5-YEAR SURVIVAL PER CENT |
| I.   Uterus not enlarged | 24 | 58 | 18 | 67 |
| II.   Uterus enlarged but not over size of 2½ mo. gestation | 40 | 55 | 54 | 61 |
| IIA. Uterus larger than 2½ mo. gestation | 7 | 0 | 9 | 45 |
| III.  Extension of carcinoma beyond uterus | 25 | 4 | 12 | 17 |
| End result, all cases | 96 | 39 | 93 | 55 |

The outlook when radiation alone must be relied upon is by no means hopeless. In fact results obtained by this method are quite encouraging. The five-year survival rate for all 96 patients treated by radiation alone is 39 per cent. However, when the patients were subdivided into clinical groups, it was found that for the 64 cases falling into Groups I and II, in which the carcinoma appeared to be confined to the uterus on clinical examination and in which the uterus was not larger than a two and one-half months' gestation, the five-year survival rate was 56 per cent.

Of the 7 patients with uteri larger than a two and one-half months' gestation, none survived five years when treated by radiation alone. It is very likely that this increased size of the uterus contributed directly to the poor clinical result by preventing adequate approximation and dosage of radium to all parts of the tumor. Since the intensity of radiation varies inversely as the square of the distance from

the source of radiation, it can readily be seen that a large uterus does not receive the same amount of radiation throughout its body from two radon capsules of given strength lying within the uterine cavity as does a small uterus. For example, it has been calculated that 3,600 millicurie hours from two radon capsules in a uterine cavity delivers approximately seven threshold erythema doses at 1.5 cm. distance, but only one threshold erythema dose at 5 cm., and one-half of a threshold erythema dose at 10 cm. from the radon capsules. Thus it is obvious that a dose which is adequate for a small uterus is totally inadequate for a large one. If the total dose is raised to compensate for this deficiency, necrosis is likely to occur in the uterine wall adjacent to the radon. With external radiation alone by means of 200 kv. x-ray we are not at present able to deliver a sufficient depth dose to cure corpus carcinoma. One must realize therefore that with present technique at least, radiation therapy may not be adequate to control bulky corpus carcinoma and should be supplemented whenever possible by complete hysterectomy. Repeated treatments of not over 1,500 millicurie hours each with three or four capsules may be the best procedure in large uteri when one is compelled to rely on radiation alone. In such cases it is understood that x-ray should also be used if possible. In a similar group of clinical Group IIA cases treated by radiation followed by complete abdominal hysterectomy the five-year survival rate was 45 per cent.

When there is clinical extension of carcinoma beyond the uterus the chance for cure is slight regardless of the method of treatment employed. Nevertheless occa-

TABLE VIII. CARCINOMA OF CORPUS UTERI. HISTOLOGIC TYPES

| HISTOLOGIC TYPE | NUMBER OF CASES | PERCENTAGE |
|---|---|---|
| Adenoma malignum Grades I and II | 95 | 48.0 |
| Adenocarcinoma Grade II | 46 | 24.0 |
| Adenocarcinoma Grades III and IV | 40 | 20.0 |
| Embryonal adenocarcinoma | 2 | 1.0 |
| Adenoacanthoma | 10 | 5.0 |
| Epidermoid carcinoma | 1 | 0.5 |
| Adenoma malignum and epidermoid carcinoma | 1 | 0.5 |
| Adenoma malignum and myosarcoma | 1 | 0.5 |
| Adenocarcinoma and myosarcoma | 1 | 0.5 |
| | 197 | |

TABLE IX. CARCINOMA OF CORPUS UTERI. RELATION OF HISTOLOGIC TYPE TO PROGNOSIS

| HISTOLOGIC TYPE | NUMBER OF CASES | 5-YEAR SURVIVAL PER CENT |
|---|---|---|
| Adenoma malignum Grades I and II | 95 | 60 |
| Adenocarcinoma Grade II | 45 | 42 |
| Adenocarcinoma Grades III and IV | 39 | 20 |
| Adenoacanthoma | 10 | 60 |

TABLE X. CARCINOMA OF CORPUS UTERI. RELATION OF HISTOLOGIC TYPE TO END RESULTS UNDER RADIATION ALONE AND RADIATION COMBINED WITH SURGERY

| HISTOLOGIC TYPE | RADIATION ALONE | | RADIATION AND SURGERY | |
|---|---|---|---|---|
| | NO. OF CASES | 5-YEAR SURVIVAL PER CENT | NO. OF CASES | 5-YEAR SURVIVAL PER CENT |
| Adenoma malignum, Grades I and II | 46 | 39 | 45 | 78 |
| Adenocarcinoma, Grade II | 29 | 41 | 16 | 44 |
| Adenocarcinoma, Grades III and IV | 18 | 28 | 21 | 14 |
| Embryonal adenocarcinoma | | | | |
| Adenoacanthoma | 3 | 66 | 7 | 57 |
| End result, all cases | 96 | 39 | 89 | 55 |

sionally something can be done as evidenced by the fact that 10 per cent of the 38 patients in the entire series which fell into this group lived five years or more. Sixty-six per cent of the patients in this advanced group died in less than one year after initial examination, whereas in the other clinical groups even though the eventual outcome was fatal only 9 per cent died in less than a year.

The five-year survival rate for all of the patients treated by a combination of radiation and surgery regardless of the particular technique employed was 55 per cent. For the cases in clinical Groups I and II it was 63 per cent. For a group of patients treated by what is now considered the most satisfactory technique, the five-year survival rate for all cases including all clinical groups was 79 per cent.

In addition to a classification according to clinical extent of disease the 197 cases on which this study is based were classified according to histologic type. Adenoma malignum Grades I and II made up nearly one-half of the total group. Adenocarcinoma Grade II was next in frequency of occurrence, being present in 24 per cent of the cases. Adenocarcinoma Grades III and IV made up 20 per cent and adenoacanthoma (a glandular tumor which has undergone squamous metaplasia), 5 per cent.

TABLE XI.  EFFECT OF RADIATION ON CARCINOMA OF CORPUS

| INTRACAVITARY RADON DOSAGE IN MILLICURIE HOURS | NO. OF CASES | COMPLETE REGRESSION | RESIDUAL CARCINOMA |
|---|---|---|---|
| 1200-2700 | 24 | 3 | 21 |
| 3000-3300 | 25 | 13 | 12 |
| 3400-4000 | 20 | 12 | 8 |
| Roentgen ray only | 6 | 0 | 6 |

An analysis of the relation of histologic type to end results and to type of treatment yielded information of considerable interest. For the entire group regardless of the method of treatment employed, the five-year survival rate for adenoma malignum Grades I and II was 60 per cent, for adenocarcinoma Grade II it was 42 per cent, for adenocarcinoma Grades III and IV it was 20 per cent, and for adenoacanthoma 60 per cent. When the results of the two methods of treatment were compared, it was found that adenoma malignum treated by radiation alone yielded 39 per cent five-year survivals; whereas 78 per cent of the patients with the same lesion treated by radiation followed by hysterectomy were alive five years or more. For adenocarcinoma Grade II, however, the difference is far less, the percentages being 41 and 44, respectively. For adenocarcinoma Grades III and IV and embryonal carcinoma the survival rate was better when radiation alone was used, 28 per cent surviving five years under this treatment and only 14 per cent when radiation was followed by surgery. Adenoacanthoma in a small series of 10 cases had a five-year survival rate of 60 per cent with no significant difference between the two methods of treatment. It should be pointed out that these figures represent results of varied techniques of treatment over a period of fifteen years. For results of the present method of treatment consult Table XII.

In 75 patients subjected to hysterectomy after intrauterine radiation, a careful microscopic examination was performed to determine the presence or absence of residual carcinoma. The effects of different doses of intrauterine radiation were determined. It was found that of six patients who received roentgen ray only, all showed residual carcinoma. In 24 cases in which the intracavitary radon dosage varied from 1,200 to 2,700 millicurie hours complete regression occurred in only 12 per cent. In 25 cases in which the dose was from 3,000 to 3,300 millicurie hours there was complete disappearance of carcinoma in 52 per cent, while in 20 patients receiving 3,400 to 4,000 millicurie hours 60 per cent showed no residual carcinoma. These results in addition to demonstrating the effect of different dosages of intrauterine radon also reveal the fact that in 40 per cent of patients receiving the largest doses (3,400 to 4,000 mc. hr.), there was evidence of residual carcinoma at the time

of hysterectomy. This is an important reason for the authors' view that whenever possible the uterus should be removed. Another important reason of course is the fact that the five-year results for radiation followed by hysterectomy are better than they are for radiation alone. The reason for the use of intrauterine radium six to eight weeks before complete abdominal hysterectomy is twofold. First, it is conceivable that radiated carcinoma even if not completely destroyed is somewhat less likely to enter blood or lymph channels or to remain as viable implants in the pelvis at the time of hysterectomy than is carcinoma which has not been subjected to radiation. Second and far more significant is the fact that the results of the combined method of treatment as now employed are definitely better than those obtained by surgery alone. This is especially true of the patients who receive 3,000 to 4,000 millicurie hours of intrauterine radiation. Of the 28 patients in our series who received this dose and who have been followed five years or more, 79 per cent survived at least five years. Arneson, following a similar plan of treatment had even

TABLE XII. CARCINOMA OF CORPUS UTERI

Intrauterine Radon 3,000-4,000 Millicurie Hours Followed in One to Four Months by Panhysterectomy

| CLINICAL GROUP | NO. OF CASES | 5-YEAR SURVIVAL PER CENT | FREE OF DISEASE 5 YR. OR MORE PER CENT | DEATH DUE TO CARCINOMA | | | DEATH FROM OTHER CAUSE IN LESS THAN 5 YEARS | LOST |
|---|---|---|---|---|---|---|---|---|
| | | | | LESS THAN 1 YR. PER CENT | 1-2 YR. PER CENT | 2-4 YR. PER CENT | | |
| I. Uterus not enlarged | 5 | 100 | 100 | 0 | 0 | 0 | 0 | 0 |
| II. Uterus enlarged but not over size of 2½ mo. gestation | 20 | 85 | 80 | 10 | 0 | 5 | 0 | 0 |
| IIA. Uterus larger than 2½ mo. gestation | 2 | 0 | 0 | 50 | 0 | 50 | 0 | 0 |
| III. Extension of carcinoma beyond uterus | 1 | 0 | 0 | 100 | 0 | 0 | 0 | 0 |
| End result, all cases | 28 | 79 | 75 | 14 | 0 | 7 | 0 | 0 |

TABLE XIII. CARCINOMA OF CORPUS UTERI

Intrauterine Radon 3,000-4,000 Millicurie Hours Followed in One to Four Months by Panhysterectomy

| HISTOLOGIC TYPE | NO. OF CASES | 5-YEAR SURVIVAL PER CENT | FREE OF DISEASE 5 YR. OR MORE PER CENT | DEATH DUE TO CARCINOMA | | | DEATH FROM OTHER CAUSE IN LESS THAN 5 YEARS | LOST |
|---|---|---|---|---|---|---|---|---|
| | | | | LESS THAN 1 YR. PER CENT | 1-2 YR. PER CENT | 2-4 YR. PER CENT | | |
| Adenoma malignum Grades I and II | 15 | 100 | 100 | 0 | 0 | 0 | 0 | 0 |
| Adenocarcinoma Grade II | 6 | 50 | 33 | 17 | 0 | 33 | 0 | 0 |
| Adenocarcinoma Grade III | 5 | 40 | 40 | 60 | 0 | 0 | 0 | 0 |
| Adenoacanthoma | 2 | 100 | 100 | 0 | 0 | 0 | 0 | 0 |
| End result, all cases | 28 | 79 | 75 | 14 | 0 | 7 | 0 | 0 |

better results in a somewhat smaller series. Ward and Sackett at the Women's Hospital in New York have found the combination of radiation and surgery more efficacious than surgery alone, as has Norris in Philadelphia. Arneson recently reviewed the literature on the surgical treatment of corpus cancer and found that of 927 reported cases 57 per cent of the patients were living five years or more.

In the group of 28 patients treated by the method which the authors now consider most desirable all of the cases of adenoma malignum and adenoacanthoma have survived free of clinical evidence of disease for five years or more. The five-year survival rate for adenocarcinoma Grade II is 50 per cent, and for adenocarcinoma Grade III 40 per cent. The five-year survival rate for the entire group of 28 cases, as stated before, is 79 per cent. Of the 28 cases 75 per cent are free of clinical evidence of carcinoma. Tables XII and XIII show the end results of recommended technique of treatment.

The patient's history will often suggest the presence of corpus carcinoma, and if so-radon is held available in the operating room at the time, a diagnostic curettage is done. If the gross appearance of the curettings is suggestive of carcinoma, a radon tandem of two or three capsules, depending on the size of the uterus, is placed within the uterine cavity immediately after the curettage. The radon capsules are each 15 mm. in length, have a combined strength of 75 to 150 millicuries, are filtered by ½ mm. of platinum and are encased in a small rubber tube the wall of which is 2 mm. thick. A frozen section is done to establish the diagnosis microscopically, and, if carcinoma is found, the radon is allowed to remain in place for a dose of 3,600 millicurie hours. The diagnostic curettage and insertion of radium are done under general anesthesia. The radon tandem is sutured in place by means of a catgut suture passed through the cervix and tied in a bow knot so that removal is not difficult. The vagina is packed with sterile gauze and a Pezzer catheter placed in the bladder. The patients are kept in bed until the radium and catheter are removed and for three or four days thereafter. Two weeks after the intrauterine application of radon external radiation by means of 200 kv. roentgen ray is given, 750 r. being given to each of four pelvic ports 11 by 14 cm. in size at a target skin distance of 70 cm., milliamperage of 30, and filtration of ½ mm. copper. One pelvic portal is treated daily or on alternate days. Six or ten weeks after the completion of radiation a complete abdominal hysterectomy is performed, the entire uterus including the cervix with both tubes and ovaries being removed. One of the first steps in the operation is the closure of the fimbriated ends of the Fallopian tubes by ligature. Care is taken to avoid trauma to the uterus and no tenaculum or forceps is placed on the body of the uterus at any time. A careful and prolonged follow-up is an essential part of the correct treatment of carcinoma of the corpus uteri.

When the diagnosis is quite definite from history and clinical examination, it is considered advisable to give the external radiation two weeks before the curettage and insertion of radium. When radiation alone is to be relied upon, another curettage should be done four to six months after the first curettage or when there is any recurrence of symptoms. If residual carcinoma is found, treatment by intrauterine radon not over 2,500 millicurie hours should be given.

In this series of cases no definite improvement in results from adding roentgen ray to intrauterine radon could be demonstrated. However, it did not appear to cause any complications and should in the authors' opinion be used to supplement radon. Since external radiation of the type described delivers only about one threshold erythema dose throughout the pelvis and since it has been estimated that from 5 to 10 threshold erythemas are necessary for control of corpus carcinoma, it is felt that the intrauterine radon is of chief importance.

Complications following the treatment of carcinoma of the corpus uteri have been few. Of the 96 patients treated by radiation alone, two developed hematuria and one had pyometra. One of the patients complaining of hematuria and dysuria had a radiation ulcer of the bladder which healed after irrigations and the instillation of argyrol. In the other no ulcer was found on cystoscopy and symptoms promptly subsided after bladder irrigations and the instillation of argyrol. The patient who developed pyometra did so one year after treatment which had consisted of the intrauterine application of 3,000 millicurie hours of radon by means of a radon tandem.

There were no complications in the group of 28 cases treated by a combination of radiation and surgery according to the plan outlined above. Among the others in the group of 93 treated by some combination of radiation and surgery there were two vesicovaginal fistulas and one rectovaginal fistula.

One of these patients had adenoma malignum with extension to the cervix when first seen. Radium was applied to both cervix and uterine cavity, the total dose being 5,400 millicurie hours. The patient also received 1,000 millicurie hours postoperatively because of some infiltration in the vaginal vault. In addition she received a pelvic cycle of x-ray both before and after operation. A vesicovaginal fistula developed four months after operation. Two years later a repair was advised but refused. The patient died six years after treatment from an unrelated cause and free of carcinoma. It is felt that overdosage of radiation was probably responsible for the development of a vesicovaginal fistula in this case.

The second patient, also a case of adenoma malignum, received first a tandem for 1,200 millicurie hours, three months later 2,500 millicurie hours, and two years later, because of recurrence, 3,600 millicurie hours. A complete hysterectomy was done two months after this last application of radium and a vesicovaginal fistula developed one year postoperatively. The fistula was closed two and one-half years after operation and there has been no recurrence. In this case also the total dose was probably excessive, although the initial dose was inadequate.

The patient who developed a rectovaginal fistula was histologically adenoacanthoma Grade III. A tandem was inserted for 3,000 millicurie hours and was followed by a pelvic cycle of x-ray. Three years later because of a recurrence of symptoms a tandem was placed in the uterus for 3,300 millicurie hours and another pelvic cycle given. A complete abdominal hysterectomy was done two months later. Three months after operation the patient developed a rectovaginal fistula. The patient is now a nine-year cure but still has her fistula. Inadequate first dose and excessive radiation after recurrence are perhaps etiologic features.

The operative mortality for the 93 patients subjected to hysterectomy following radiation therapy was 4.3 per cent.

The principal cause of death in the entire group of 197 cases was residual or recurrent carcinoma in the pelvis about the vaginal vault, causing hemorrhage or obstruction of the ureters with resultant uremia. Four cases had pulmonary metastases proved by x-ray, one of these cases had metastasis to a cervical node proved by biopsy. Two patients died of carcinoma primary in another part of the body and apparently unrelated to the corpus cancer. One of these developed carcinoma of the breast twelve years after hysterectomy and died of carcinoma of the breast two years later. The other died of squamous carcinoma of the vulva six years after radiation and hysterectomy for adenocarcinoma of the corpus uteri.

## SUMMARY AND CONCLUSIONS

1. Carcinoma of the corpus uteri is in most instances a postmenopausal disease, uterine bleeding its most constant symptom.

2. Postmenopausal bleeding should at once suggest the presence of carcinoma of the corpus even though the patient has a readily palpable fibromyomatous uterus. These two conditions were found to be associated in 38 per cent of the cases in this series.

3. Pain would appear to be an important prognostic factor. Sixty-six per cent of the patients complaining of pain at the time of first examination later died of carcinoma. In nearly half of these, initial examination revealed no evidence of extension of carcinoma beyond the uterus.

4. The 197 cases of carcinoma of the corpus uteri on which this study has been based fall readily into three principal histologic groups.

Approximately one-half of all cases were adenoma malignum, one-fourth were adenocarcinoma Grade II, and approximately one-fourth adenocarcinoma Grade III or IV. The histologic type bears a direct relation to chance for cure and is of definite prognostic importance. The five-year survival rate for adenoma malignum is appreciably higher than for adenocarcinoma Grade II and, that for adenocarcinoma Grade II is higher than for adenocarcinoma Grades III and IV. The results in a small series of cases of adenoacanthoma indicate that the prognosis in this group is very nearly equal to that for adenoma malignum.

5. It appears worthwhile from both a prognostic and a therapeutic standpoint to subdivide the cases into clinical groups according to size of uterus and palpable extent of disease. If the uterus is not larger than the size of a 2½ months' gestation and if there is no evidence of extension of carcinoma beyond the uterus, the five-year survival rate is 60 per cent if based upon the entire series of 197 cases without regard to method of treatment, and 88 per cent if based on results in a smaller series of cases treated according to what is regarded by us as the preferred method of treatment. If the uterus is larger than a 2½ months' gestation our findings indicate that the chance for cure from radiation alone is extremely low. If there is palpable extension of carcinoma beyond the uterus the chance for five-year survival is approximately 10 per cent.

6. Radiation alone has definite curative value in cases which for one reason or another cannot be subjected to subsequent panhysterectomy, the five-year survival rate for the group of 96 patients treated by radiation alone being 39 per cent. When only clinical Groups I and II are considered the five-year survival is 56 per cent and the five-year cure (free from all evidence of carcinoma five years or more) is 47 per cent.

7. Intrauterine radon, usually not less than 3,600 millicurie hours, supplemented by roentgen ray and followed by panhysterectomy seems to offer the greatest opportunity for cure. Seventy-nine per cent of the patients so treated have survived five years or more and 75 per cent have been free from all evidence of carcinoma for over five years. The risk of any major complication under this plan of treatment seems to be slight.

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121 EAST SIXTIETH STREET

### DISCUSSION

DR. JAMES A. CORSCADEN.—The best method for treating cancer of the corpus has not been established. Stoeckel of Berlin reports about the same percentage of five-year cures by vaginal hysterectomy and Wintz reports similar figures from x-ray alone.

From our own experience with 144 cases several points may be noted. 25 per cent of the women were unmarried; 43 per cent were nulliparous as compared with 14 per cent for our cancers of the cervix. The average weight of the patients in the corpus cases was 165 pounds and of the cervix cases 128 pounds. Age should influence us little in diagnosis inasmuch as in Dr. Healy's series 15 per cent and in ours 20 per cent were below the age of fifty.

Our clinic is trying to figure out some endocrine predisposition. However, there is a large number of these women who have small hands and feet and large hips. This in connection with the childlessness and low marriage rate is of interest.

We have twenty-one uteri obtained by hysterectomy after previous radiation and in eight of those there was no cancer found. On the other hand, in some cases in which the uterus seemed to be free of cancer, there was a small metatasis in the ovary. These two simple findings lend weight to the mode of therapy advocated. The preliminary radiation gets rid, at least, of the local implantation metastases. The hysterectomy eliminates metastases in the ovaries and those adjacent to the uterus when the glands are not yet involved.

In regard to results: we have only 10 cases which have been treated more than five years both by preliminary radiation and hysterectomy. One of them died in the hospital (an operative death), one other patient died of carcinomatous metastases, and the other eight lived.

Our procedure in the management of uterine bleeding at the menopause age is at present as follows:

I. Determine operability of the patient
    A. General:
                Circulatory, excretory, respiratory
                Constitutional (obesity, senility)
    B. Local
                Technical (obesity, accessibility)
                Extent of disease
II. Determine acceptability of artificial menopause
III. In the operating room
    A. Curettage of cervix (specimen)
    B. Curettage of endometrium (specimen)
        Precise determination of source of curettings
            Specimens (1) in formalin for an 8-hour report
            Specimens (2) in Zenkers (permanent preparation)
    C. Radium is inserted as for carcinoma of corpus
IV. A. The 8-hour pathologic report is "benign": Radium remains for a dose of
          2,400 mg. hr. (Sterilizing dose)
    B. The 8-hour pathologic report is "malignant"
      (1) The operative risk is slight
        (a) Radium remains for a dose of 3,000-3,600 mg. hr.
        (b) Complete abdominal hysterectomy 5 weeks later
        (c) Roentgen therapy about one month later
      (2) The operative risk is great or the disease extensive
        (a) Radium remains for a dose of 5,000 mg. hr.
        (b) Roentgen therapy about a month later

DR. THOMAS C. PEIGHTAL.—Worthy of note in this paper is the statement that such criteria as size of the uterus and presence or absence of pain are useful factors in clinically classifying and estimating prognosis in these growths. Also of interest is the fact that patients with Grades III and IV carcinomas did no better with hysterectomy than with radium alone. This paper rightly stresses the importance of a technique which aims, in so far as possible, to place the radium in contact with the entire uterine cavity, and which by spacing x-radiation, radiation and surgery sufficiently far apart thus avoids too great depletion of the patient's strength before the hysterectomy is done, a matter for careful consideration if the usual operative mortality in this elderly age group is not to be increased.

In checking over briefly the end results in 172 cases of corpus carcinoma on the Gynecological Service of the Roosevelt Hospital from 1910 to 1933 it is of interest to note that the five-year cure rate has definitely improved as more and more cases have had radiation in conjunction with hysterectomy. From 1910 to 1925 surgery alone was used almost uniformly, 80 per cent of cases were considered operable and the absolute five-year cure rate for the 90 cases of this period was only 26 per cent. From 1926 to 1929 some of the 49 cases admitted had radium and high voltage therapy either preoperatively or postoperatively. Of these, seven, well advanced, received radium alone and none lived five years while in the 42 with hysterectomy there was an absolute five-year cure rate (for the whole 49 cases) of 41 per cent. From 1930 to 1933 increasingly more cases were treated with radium alone plus high voltage therapy and more cases had prehysterectomy radiation. Of the 33 cases in this period 20 had hysterectomy and 13 received combined radiation only. The absolute five-year cure rate in these two groups (based on the total 33 cases) was 43 per cent and 23 per cent, respectively. In the past three years nearly all operable cases have received radiation in conjunction with hysterectomy, and we feel confident that the marked improvement in prognosis amply justifies the added time and inconvenience which proper preoperative radiation entails.

DR. NELSON B. SACKETT.—At the Woman's Hospital we have had 123 patients who have been followed five years or more, of which 115 were treated. Of that number, 56 are still alive, a five-year survival rate of 45.5 per cent absolute, and 48.7 per cent relative. I have studied our ten-year results in a small series of 30 cases, of whom 9, or 30 per cent, survived for ten years. If we add one patient who died after a strangulated hernia operation and who on autopsy showed no carcinoma, and another patient who died of apoplexy and in whom no carcinoma was found at autopsy, the ten-year survival rate is 36.6 per cent. We say ''survival'' even at ten years, because we have had two or three patients who survived ten years or more and who have since died of undoubted carcinoma.

We subscribe to Dr. Healy and Dr. Brown's conclusion that the combined therapy is best. Radiation alone gives us 34 per cent and the combined treatment gives 67 per cent, of five-year relative survivals. In operable cases, radiation alone gives a 45 per cent relative survival rate. Since at least one out of three hysterectomy specimens shows cancer persistent after radiation, the uterus should be removed whenever possible.

Our excellent results in cases of adenoma malignum make us wonder whether we are in this condition dealing with malignancy or not. Following one curettage in a recent case the pathologic diagnosis was adenoma malignum with some invasion of the stroma. A granulosa cell tumor had been removed by laparotomy at the time of this curettage. Six weeks later, a second curettage was done and the specimen showed almost complete obliteration of the marked glandular hyperplasia of the first specimen and no malignancy whatsoever. In a second case, I did a curettage and radium insertion for adenocarcinoma of the uterus, Grade III, with invasion of the uterine wall. This was followed later by panhysterectomy, and removal of a granulosa cell tumor. The uterus showed complete disappearance of the marked glandular hyperplasia found in the first specimen.

DR. W. P. HEALY.—One is amazed, if he studies the patients that come with carcinoma of the corpus and coincident pain but with no evidence of metastatic involvement, to find that these apparently favorable cases fail to survive for five years. Coincident involvement of the cervix in a case of primary cancer of the corpus is also of bad prognostic significance.

Since it gives such good end results, we have long thought that adenoacanthoma is just the result of metaplasia in adenoma malignum. Corpus cancers can be divided into two main groups, (1) the adenoma malignum type of case, in which the cancer occurs in bundles of glands piling up into the uterine cavity, and slowly invading the myometrium, but never breaking through the basement membrane, and (2) adenocarcinoma, which is the same type of growth plus free cancer cells in the stroma. There is a genuine difference in the prognosis of the two histologic groups.

I am inclined to believe, as Dr. Peightal remarked, that we might possibly omit hysterectomy in the Grade IV and embryonal types of cancer without disadvantage.

We have been much impressed with the fact that less than 3,300 millicurie or milligram hours of intracavitary radiation does not accomplish all one might hope for.

If you have a patient, in whom you are going to restrict treatment to irradiation methods, I would be inclined not to go above 3,600 millicurie hours with two, three or four capsules, according to the length of the canal, for the first treatment. Three months later, I would repeat the curettage and insert radium, in a small dose, we will say, of 2,000 hours. By all means add roentgen therapy, because one of the common forms of metastatic involvement in cancer of the corpus uteri is the lymphatic extension to the ovaries which will result in large ovarian tumors.

Radiation is a strain on these patients. I always tell the family that the patient is to undergo two major procedures. Irradiation is the first and it will, in my opinion, be fully six weeks after the last radiation treatment is given before she will be well enough to undergo hysterectomy. I find even that my tendency in the last year or more is to increase to eight weeks, instead of six weeks, the interval before hysterectomy is done.

In a considerable percentage of cases we find that there is little or no uterine cavity. There is instead a large mushy overgrowth of cancer, and no large cavity in which you can place capsules in various directions. For that reason we do not believe in trying to pack the uterine cavity with radon or radium tubes. Heyman admitted to me packing could not be done in every case, but, theoretically, he thought it a good thing to do if possible. Burnam, on the other hand, told me that he had given up this method and was simply using tandem applicators in the canal, as we do it at the Memorial.

We find that in about two out of three of our cases there is no evidence of cancer in the uterus when we take it out eight weeks after radium. On the other hand, since in one out of three there is residual tumor we must take the uterus out in all cases. This is also the reason why when we are going to treat a case with radiation only, three or four months after the first series of treatments with radium and x-ray, if the uterus remains heavy and large and if there is persistent uterine discharge, we re-investigate the interior of the uterus.

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**Keller, R., and Limpach, J.: The Pre- and Postoperative Use of Transfusions of Placental Blood at the Strasbourg Maternity,** Gynéc. et obst. 37: 173, 1938.

In view of difficulties in procuring donors, these writers resorted to the routine use of placental blood. An advantage of using this blood lies in the high content of erythrocytes, leucocytes, hemoglobin, and the presence of several hormones. The placental blood only of healthy, Wassermann-negative patients is used. A detailed description of the entire technique is given. Approximately 60 to 90 gm. (rarely 100 to 150) of blood are obtained at each birth.

When required the blood is heated to 38° by placing the flask in a water bath, then filtered through three thicknesses of sterile gauze into a sterile graduate that has been previously rinsed with physiologic saline.

The use of transfusions of placental blood in the treatment of the sickness following deep x-ray therapy has been efficacious, and it is enthusiastically recommended.

ARNOLD GOLDBERGER

# ERYTHROBLASTOSIS FETALIS AS A CAUSE OF FETAL MORTALITY*

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FOR some years it has been recognized that the condition known as hydrops fetalis is a cause of death in late fetal life, or immediately after birth. Fatal icterus of the newborn, as its name implies, is a cause of death shortly after birth and, judging from reports in the literature, is fortunately rather rare. In recent years these two conditions, together with some cases of congenital anemia, have been grouped under the heading of erythroblastosis fetalis, a condition in which the fetus or newborn child exhibits a marked degree of blood destruction and blood regeneration, which may be accompanied by any or all of the following: anemia, jaundice, general edema of the tissues and placenta, fluid in the body cavities, enlarged spleen and liver, yellow amniotic fluid and vernix caseosa. There is no general agreement among investigators as to whether the blood destruction is a primary factor, or whether it follows upon an abnormal type of blood production in which very early forms of the red and white cell series are found circulating in excess in the blood stream.

The histories of mothers giving birth to hydropic infants reveals an unusually high number of miscarriages, premature births, stillbirths, and births of macerated fetuses. Although this fact is noted, it has not been emphasized that these products of conception are probably examples of the same pathologic condition as are the outspoken cases of hydrops or icterus. Moreover, the possibility that many stillbirths or premature births of apparently normal infants in a family in which neither hydrops nor icterus has occurred, may be due to erythroblastosis has not received any attention. An article by Javert emphasizes that this condition is a potent cause of infant mortality, and points out that many infants who are apparently normal, but who die within the first two weeks of life without any evident jaundice or anemia, are really cases of erythroblastosis as revealed by autopsy. I wish to call attention to the probability that this disease is responsible for the death of an undetermined percentage of infants who are outwardly normal, and who are listed as stillbirths, in which there appears to be no obvious cause of death although occasionally perhaps there is difficult labor. If there is no history of hydropic or icteric infants in the family to call the attention of the obstetrician to the possibility of a definite pathologic basis for the stillbirth, an autopsy probably is not done, and the diagnosis is missed.

I wish here to report two diagnosed cases of erythroblastosis fetalis in stillborn infants, who were regarded as perfectly normal by the obstetrician and by the pathologist who examined them externally. In both cases the infant was definitely overweight, a fact which apparently should suggest the possibility of erythroblastosis, according to Javert. One was premature, one, full term. There was no evident jaundice in these infants; both were pale; one had hemorrhagic areas over the skin of the thighs and one had a scrotum tense with fluid, which collapsed when the abdominal cavity was opened. The placenta was not stated to be large in either case, and its size was mentioned as being normal in the case of the 14.5 pound infant. Both were regarded as victims of the hazards attending birth, delivery of the shoulders having been difficult in both cases. These two infants constituted two of the only three apparently normal full-term or almost full-term infants received into the embryology laboratory in a period of two years, inasmuch as the obviously defective ones are retained in the pathologic laboratory either for specimens, or for autopsy. That two of the three should prove definitely to be cases of erythroblastosis, suggests that an appreciable number of stillbirths at or near term that appear to be normal may be due, in fact, to erythroblastosis. Javert found this condition to be a more frequent cause of neonatal death than was syphilis.

CASE 1.—Baby C.* The obstetric history of the mother was that she had had five previous pregnancies 18, 15, 13, 8, and 5 years before, all normal and going to full term. The largest child weighed 10.5 pounds at birth. The mother was very obese, weighing 238 pounds. The sixth pregnancy was terminated by induction of labor at eight and one-half months because of the size of the fetus, and the increasing blood pressure of the mother. The head was delivered with little difficulty, but the shoulders were so broad that they had to be delivered by means of a hook. The weight of the child, which was dead, was 14.5 pounds. There was no apparent edema of the placenta or of the infant except for the fluid in the scrotum previously referred to. The child was regarded as normal, death being due to difficult delivery. Dissection revealed a rather amazing picture. The organs were enlarged far more than would be expected even in a 14.5-pound child. As will be seen from Table I and Fig. 1 the organs were all above normal weight. The black column represents the relation of the weight of the organs of this fetus expressed in percentages of

TABLE I. WEIGHT OF ORGANS IN TWO CASES OF ERYTHROBLASTOSIS

|  | BABY C. 8.5 MO. | NORMAL† | BABY B. FULL TERM |
|---|---|---|---|
| Heart | 66.0 gm. | 17.0 gm. | 35 gm. |
| Liver | 1,120.0 gm.* | 78.0 gm. | 321 gm. |
| Spleen | 20.0 gm. | 8.0 gm. | 18 gm. |
| Thymus | 18.0 gm. | 13.7 gm. | 27 gm. |
| Lungs | 79.0 gm. | 39.0 gm. | 100 gm. |
| Kidneys | 36.5 gm. | 27.0 gm. | 43 gm. |
| Adrenals | 23.5 gm. | 5-6 for adult‡ | 33 gm. |
| Fetus | 14.5 lb. | 7.5 lb. | 11 lb. |

*A piece of liver estimated as 1/10 to 1/7 of the entire liver, containing the entrance of the umbilical vein, weighed 160 gm. The remaining liver was discarded before its weight was ascertained.

†Normal weights taken from Mallory's *Pathological Technique*, 1938.

‡No weight for adrenals at birth was given.

*I wish to express my thanks for this specimen and for the obstetrical history to Dr. Evan Shute of London, Ontario.
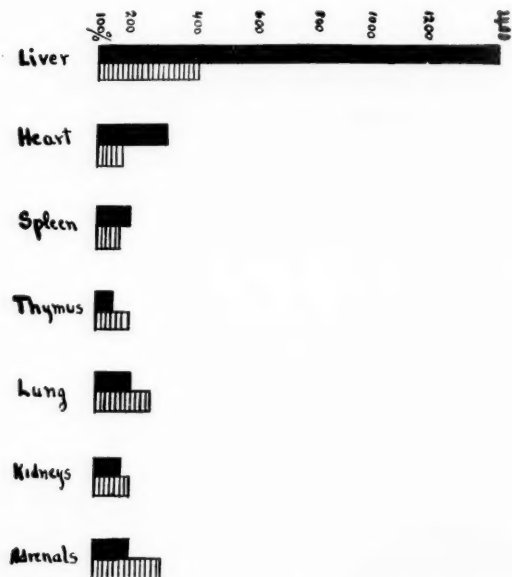
Fig. 1.—Weights of organs of two cases of erythroblastosis expressed as percentages of normal weights. The base line is taken in each case as 100 per cent of the normal weight of the organ in question. The solid black columns are the weights of the organs in Case 1; the lined columns those of the organs in Case 2.



Fig. 2.—Section of liver of Case 1. Note the numerous areas of hemopoiesis, the crowding of the cords by the sinusoids filled with blood cells mature and immature, with a consequent loss of normal liver topography. ×195.

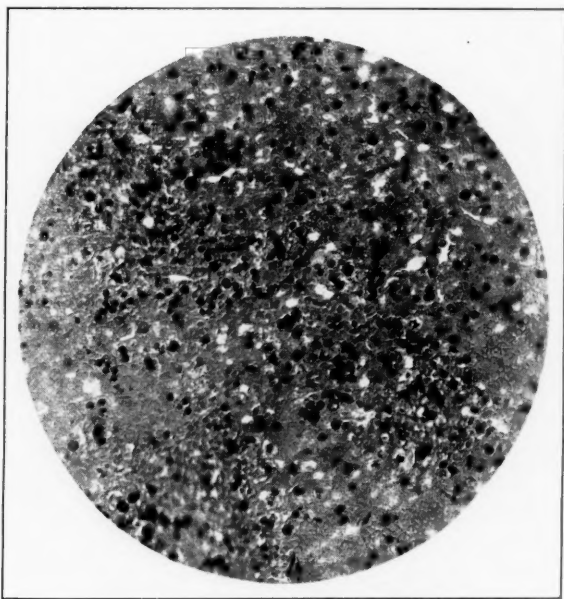the normal weight of the organs of the newborn, the base line being 100 per cent in each case. The lined column deals with the weight of the organs of the second case to be reported. Note that the liver was 14 times its normal weight, the heart nearly four times as heavy as normal; while spleen, lungs, and adrenals were approximately 200 per cent of their normal weight; thymus and kidneys being about 150 per cent of the normal weight.

*Liver.*—The liver was tremendously enlarged. The dissector who was preparing the fetus for embryologic demonstration threw away most of the liver, keeping only a narrow segment where the umbilical vein entered. This narrow slice, estimated variously as about one-tenth to one-seventh of the entire liver, weighed 160 gm. The liver would have weighed then according to the most conservative estimate at least 1,120 gm. Areas of hemopoiesis were far more numerous than in the normal
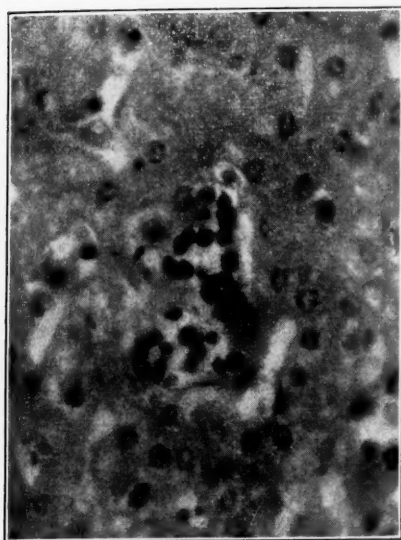


Fig. 3.



Fig. 4.

Fig. 3.—Section of a full-term fetal liver as control. Although areas of hemopoiesis are present, they do not crowd the sinusoids, and the normal liver pattern is apparent. ×400.
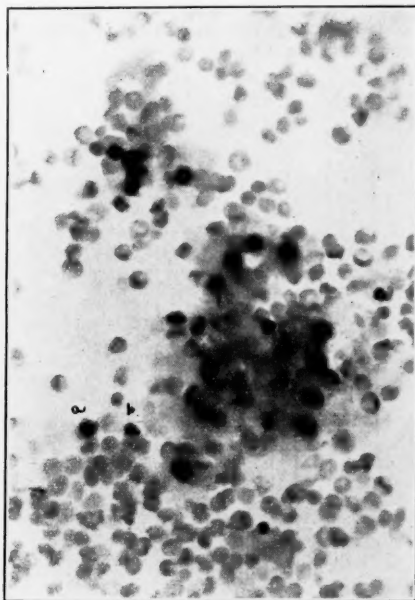
Fig. 4.—Blood smear from 8.5 months' fetus with erythroblastosis fetalis (Case 1). As the blood had clotted, it was impossible to make a good smear. The stem cells and nucleated reds tend to clump in a thick mass, one of which is seen in the center of the field; hence parts of it are out of focus. *a* and *b* are two nucleated red cells, *a* with a single large nucleus, *b* with a nucleus fragmented into three parts. There is a wide variation in size among the red cells. ×400.

liver. Fig. 2 shows the section of liver of this fetus, with many areas of blood formation, most of the nucleated cells being of the red series. The sinusoids were crowded with blood cells, and the liver cords were so compressed by blood as to be almost unrecognizable. The contrast between this and a picture of the liver from a full-term normal fetus, in which the liver cords are well defined, the cell boundaries clear, and only occasional areas of blood formation are present, is brought out in Fig. 3. Seventy per cent of the nucleated cells in the blood stream in the liver were nucleated red cells. Only 2 per cent of the nucleated cells in the circulation were mature white blood cells, the remaining 28 per cent being immature stem cells, mostly of the erythrocyte series. Fig. 4 shows a field of blood from this fetus. Because the blood was not fresh when the smear was made, it is poor as a smear, but shows a group of nucleated red cells. These tend to clump together. The variation in size is well shown in this smear.

Evidences of blood destruction were found in the masses of bile pigment which crowded the cells and capillaries, not only of the liver, spleen, adrenals, and kidneys but also of the lungs. These are seen as small black dots in Fig. 2. No iron was found in the cells by the Prussian blue method. This baby, had it lived, would doubtless have developed either fatal icterus, from which it would probably have succumbed, or congenital anemia.

Because this baby showed no iron in the liver, it might be denied inclusion into the category of erythroblastosis by those who insist that only those cases showing hemosiderin in the liver cells be included in this classification. Ferguson has described cases of erythroblastosis without jaundice, or edema, and which contained bile pigment but no iron in the liver cells.

*Heart.*—The heart weighed 66 gm., almost four times the normal weight. The left ventricular wall, usually thinner than the right in the fetus, was as thick as the right; and both were much hypertrophied, being 11 mm. in thickness. The thickness of the ventricular walls in the adult are given by Delafield and Prudden as 0.4 to 0.6 cm. for the right ventricle, and 1.6 cm. for the left. In this infant, the hypertrophy of the right ventricle was due to a stenosis in the ductus arteriosus; that of the left apparently was due to the impediment offered to the blood flow by the erythroblastic foci in the capillaries of the different organs. There was scarcely any lumen in the left ventricle, so hypertrophied were the walls.

*Spleen.*—The spleen which weighed 20 gm. showed areas of erythroblastosis. Although the lymphoid follicles are not thought to be as prominent as usual in cases of erythroblastosis fetalis, there were definite large follicles about the arteries in this spleen. The congestion was so marked that little of the normal architecture of the spleen, apart from the lymphoid follicles, was evident; the sinusoids being so distended with red blood cells and erythropoietic foci as to leave little of the splenic cells visible. Bile pigment, free and in cells, was abundant.

*Kidneys.*—These weighed 38.5 gm.; the blood vessels were dilated and filled with blood cells. In the capillaries, these were packed tightly, and had not taken up the stain although in nearby large blood vessels, the red cells were brilliantly colored. The explanation of this is not clear; the discs appeared as mere ghostly forms devoid of all hemoglobin content. The outermost zone of the medulla and the glomeruli were rich in hemopoietic foci; the intracapsular space being crowded with immature forms with dense nuclei and little cytoplasm. Bile pigment was abundant.

*Adrenals.*—The adrenals which weighed 23.5 gm. showed some congestion. There was bile pigment in the cells and in the capillaries, especially of the zona fasciculata. Extrahepatic formation of bile pigment was apparently going on in this fetus, with deposition of bile pigment throughout the organs. Most of the tissue especially of the zona fasciculata was degenerate, the remaining cells were large and brilliantly stained with the eosin.

Here then is a case in which there is erythroblastosis, in which there is hypertrophy of heart, liver, and spleen, in which there is excess production of bile pigments but in which there is no evidence of iron in the liver cells. Jaundice would probably have occurred after birth when the burden of increased blood destruction normal to the newborn was thrown upon liver cells already compressed and filled with bile pigments.

*Brain.*—The brain showed marked congestion of the superficial vessels but no hemorrhages. There was no evidence of bile staining in any of the brain tissue, when examined in slices about 5 mm. in thickness.

CASE 2.—Baby B. This case was the next outwardly normal fetus at or near full term brought to the embryology laboratory. The obstetric history of the mother is as follows: Full-term child, now 17 years old. Second pregnancy, a stillbirth. Third and fourth pregnancies, normal full-term children alive and well. Fifth pregnancy a miscarriage. Sixth, a normal full-term child. Seventh a miscarriage. Eighth, stillbirth at term, subject of this report. Weight at birth 11 pounds. The baby was pale, and the skin had hemorrhagic spots over the arms and legs. It appeared normal, except for the pallor and the size. I suspected, with the history

of miscarriages and stillbirths, and the large size of this baby, that it too might be a case of erythroblastosis. At autopsy, the organs were enlarged, as shown by Fig. 1 and Table I. The relative weights of the organs of this infant compared with the normal as 100 per cent are shown in the horizontally lined columns. The liver in particular is over-weight. The thymus and lungs both had petechial hemorrhages over the surface, and weighed far more than normal. The brain of this infant as in Case 1 showed marked congestion of the superficial vessels; but no evidence of intracranial hemorrhage or of icterus. The organs showed excessive erythropoiesis.

*Liver.*—The liver which weighed 321 gm. showed great congestion, the sinusoids being blocked in many cases by hemopoietic areas as well as by mature red blood cells. The liver cords were compressed by these distended sinusoids until almost all semblance of liver was lost (Fig. 5). The periportal spaces were crowded with young blood cells. The liver cells themselves were large and coarsely granular.
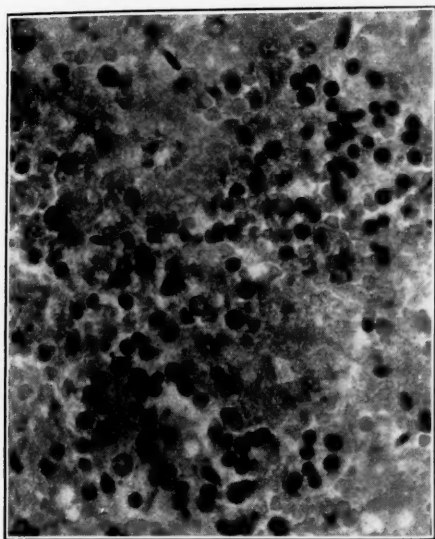


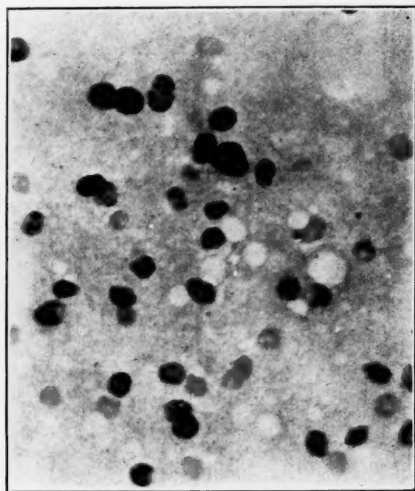Fig. 5.                                    Fig. 6.

Fig. 5.—Liver of a full-term fetus with erythroblastosis fetalis (Case 2). Note the prominent areas of hemopoiesis, the loss of liver architecture through compression of the liver cords by red blood cells and hemopoietic areas in the sinusoids. Compare with Fig. 3.  ×400.

Fig. 6.—Blood smear from a full-term fetus with erythroblastosis fetalis. Note the small number of erythrocytes, and the great profusion of nucleated cells, most of which are immature cells of the granulocytic series.  ×400.

In some areas the cytoplasm was practically gone, the only occupant of the cell being the nucleus which was as large as 18 micra across. There was a large amount of bile pigment in the hepatic cells as well as free in the blood vessels. No iron was found in the hepatic cells when they were treated by means of the Prussian blue reaction. This was also true of all the organs examined.

*Blood.*—In areas of hemopoiesis many of the nucleated blood cells possessed a cytoplasm which stained like that of mature red blood cells. Other cells, smaller than those with dense nuclei, and very little protoplasm, suggested stem cells. Immature white blood cells were found in the blood vessels. Of 374 cells found within the blood vessels in the liver, 38, or 10 per cent, were nucleated. In a count of 120 nucleated cells, 60, or 50 per cent, were definitely nucleated reds, and 19, or 16 per cent, were mature white blood cells. The remaining nucleated forms were either the primitive stem cells, or myeloblasts. Fig. 6 shows an area from a blood smear which is composed of red cells and a group of myeloblasts. Because of the fact that the

blood was not obtained until eighteen hours after death, the smear is poor. Here there are far more nucleated than nonnucleated cells. The estimate of the percentage of cells which were nucleated was made from cells in a blood vessel rather than from the smear because of the uneven distribution of cells in the latter.

Numerous red blood cells were found with large holes in them as if the nuclei had just been extruded. The cells varied markedly in shape as well as in size, ranging from 4½ to 9 micra. White blood cells, rather rare in the mature form, varied from 6.8 to 12.9 micra. Platelets were extremely rare which might account for the hemorrhagic tendencies noted in these children.

*Heart.*—The heart weighed 35 gm. The heart cells, as well as the blood vessels, had an abundance of bile pigment in them.

*Spleen.*—The spleen weighed 18 gm. The lymphoid follicles were quite definite. Bile pigment was noted in the cells and free in the blood vessels. The endothelial lining of the capillaries and blood vessels were unusually prominent, forming a quite thick layer. Frequent megakaryocytes were seen.

*Adrenal.*—The adrenals weighed 33 gm., were extremely friable, so that it was almost impossible to pick them up. The adrenal sinusoids were packed with blood. The zona fasciculata was filled with huge eosinophilic cells whose lightly staining nuclei possessed a thin chromatin network. These eosinophiles grew more frequent in the reticular layer and the medulla where they, together with huge sinusoids, filled the latter structure. These cells averaged 33½ micra in diameter. Throughout the adrenal there were areas of hemopoiesis, and also areas in which bile pigments were abundant.

*Pancreas.*—The pancreas showed no areas of marked blood formation and some amount of bile pigment. The Prussian blue reaction was negative.

*Kidneys.*—The kidneys weighed 43 gm. Their glomeruli were filled with dark nucleated cells as was true in the first case. In some areas there were very large eosinophilic cells in the convoluted tubules which stood out with unusual distinctness.

Here then were two fetuses, which were definite cases of erythroblastosis fetalis, with no outward sign of abnormality except undue size and that the fetus was supposed to have died in each instance due to prolonged delivery because of this. It may indeed have been a factor, but inasmuch as erythroblastosis is known to cause death when accompanied before birth by hydrops, and after birth by jaundice, even in normal-sized infants, it is not unreasonable to suppose that this was the primary factor in causing fetal death in these cases. It is impossible to say how many stillbirths of infants at or near term can be attributed to this condition until some large obstetric clinic routinely examines at autopsy all products of conception. Javert suggests that all infants weighing over 1,500 grams who die in the first two weeks of life be examined at autopsy for this condition, he having found 4.5 per cent so affected in a series of 110 such cases. I would suggest that *all* fetuses within the viable period that are born dead or succumb shortly after birth be examined for the presence of erythroblastosis whether they be outwardly normal or not, in order still further to ascertain the importance of this condition in causing the death of infants either before or during birth; also, in families in which there is no evidence of syphilis, or any cause for repeated miscarriage that products of conception born before the viable period be examined in order to determine how early in fetal life this condition may arise.

Transfusion is helpful in these cases, and it is possible that where the obstetrician has cause to suspect that the infant may have erythroblastosis because of a family history of the condition, early induction of labor while the fetus is still viable, followed by immediate trans-

fusion may reduce the mortality of this group of infants. It is not improbable that the obstetrician has frequently received blame for poor management of a case because the child was born dead, when in reality, the blame should have been placed on the pathologic condition from which the child suffered.

I have suggested (1937) that erythroblastosis is due to a dominant mutation in one of the primitive germ cells of one of the parents, and that all subsequent germ cells derived from this original one would possess the mutated gene, so that approximately half the children would be affected in a series of families in which this occurs. Darrow (1938) has stated that she believes it to be due to a sensitization of the mother to fetal hemoglobin during a pregnancy, through the escape of fetal blood into the maternal blood stream, with a subsequent hemolysis of the fetal blood as the antibodies pass back through the placenta into the fetal circulation. She states that this explains the fact that all children born after the time when the first one develops erythroblastosis will have the same condition, as the mother retains the antibodies which cause hemolysis of the fetal blood. The obstetric history in the second case is not in agreement with such a theory, inasmuch as several normal children were interspersed between the stillbirths and miscarriages in this family. It is true that the others were not proved cases of erythroblastosis, but in these families it is probable as Darrow admits, that all miscarriages and stillbirths are to be regarded as evidences of this condition.

I have reviewed much of the literature dealing with cases of erythroblastosis and have found that there are enough families reported in which normal children followed the child with erythroblastosis to make it apparent that the rule which Darrow calls attention to is by no means infallibly followed; namely, that once a child in a family has exhibited this condition all subsequent children will be affected. There are a few records of twins born, one normal, one affected, which also make it questionable whether Darrow's explanation can hold in all instances, for circulating antibodies in the mother's blood stream should affect both twins equally. Table II lists cases in which normal children followed the birth of one with icterus gravis or hydrops, and some, such as Cohn's in which normal children were interspersed between two hydropic infants, so that the criticism cannot hold here, that perhaps the antibodies in the mother's blood had lost their potency and so enabled a normal child to be born after the first one with hydrops. Table III gives the instances in which twins were born, one said to be normal, the other affected.

It is true that in some of the cases listed in Table II, the diagnosis was not confirmed by autopsy, and so it might be objected that the cases may not have been true erythroblastosis fetalis. The family history of miscarriages, stillbirths, infants dying within a few days of jaundice or with convulsions and with no evidence of syphilis is one that so far has not been duplicated in other conditions hence such an extensive history is reliable evidence, in most instances, of erythroblastosis fetalis especially when the disease is outspoken in one of the later children in the family.

TABLE II

| AUTHOR | ORDER OF BIRTH | REMARKS |
|---|---|---|
| Abt | 1. Died 3rd day of jaundice<br>2. Eight months stillbirth<br>3. Died pneumonia twelfth day<br>4. Died fourth day of jaundice<br>5. *Normal male*<br>6. Jaundice, transfused, recovered<br>7. Premature, jaundiced, died on second day | |
| Astrachan | 1. Intense jaundice, recovered, died 2 months, with paralysis<br>2. Died fifth day of jaundice<br>3. *Normal male aged 10 years*<br>4. Died fourth day jaundice<br><br>5. Died on third day jaundice<br>6. Jaundice, given maternal serum, recovered | Probably cerebral symptoms due to lesions occasioned by jaundice<br><br><br>Pathologic picture of erythroblastosis fetalis<br>Same pathologic picture |
| Ritter cited by Ballantyne | 1, 2, 3. Normal<br>4. Child with hydrocephalus and large placenta<br>5. *Normal*<br>6. Hydrops | Large placenta suggests presence of erythroblastosis |
| Löhlein cited by Ballantyne | 1. Normal, died 4 years meningitis<br>2. Died of fits at 6 mo.<br><br>3. Died early of general weakness<br>4. Premature, 36 weeks, hydrops<br>5. *Normal infant* | Suggestive of cerebral symptoms of kernicterus |
| Brockwell | 1. Normal<br>2-9. Two were miscarriages, six were jaundiced, of whom one died<br>10. *Normal* | |
| Cohn cited by Ballantyne | 1-5. Miscarriages<br>6. Hydrops<br>7. *Normal*<br>8, 9. Hydrops | |
| Diamond and others | 1, 2. Normal<br>3. Anemia, jaundice, transfused, recovered<br>4. *Normal*<br>1. Died of jaundice first day<br>2. Jaundice, anemia, transfused, recovery<br>3. Normal | |
| Dorff and Shapiro | 1. Died with erythroblastosis fetalis at 1 day<br>2. *Normal* as far as this condition is concerned | |

TABLE II—CONT'D

| AUTHOR | ORDER OF BIRTH | REMARKS |
|---|---|---|
| Fordyce and McAfee | 1. Normal male<br>2. Died 2 months of jaundice<br>3. Died first day of jaundice<br>4. *Normal male* | |
| Hampson | 1. Normal male<br>2-9. Died before 3 days jaundice<br>10. *Normal female*<br>11-14. Died before 3 days<br>15. Jaundiced, recovered<br>1-7. Died of jaundice<br>8-10. Miscarriages<br>11-13. *Living and well* | Last 3 of 13 pregnancies normal |
| Hawksley | 1-3. Normal<br>4. Stillbirth<br>5. Died 2 months jaundice<br>6. *Normal*<br>1. Jaundice male died 3 months<br>2. Miscarriage<br>3. *Normal* | Bile ducts were patent |
| Hellman and Hertig | 1. Normal<br>2. Hydrops<br>3. *Normal* | Born 1 year after hydropic fetus |
| | 1, 2. Normal<br>3, 4. Miscarriages at 6 weeks<br>5, 6. *Normal*<br>7. Hydropic female<br>8. Ectopic pregnancy<br>9. *Normal*, alive and well<br>1, 2, 3. Normal<br>4. Hydrops<br>5. *Normal*<br>1. Normal<br>2. Died 3 months of convulsions | In view of later family history, may have been case of kernicterus |
| | 3, 4, 5. *Normal*<br>6. Died fourth day of jaundice<br>1. Normal<br>2. Died second day jaundice<br>3. *Normal*<br>1-5. Normal<br>6. Jaundice, erythroblastosis<br>7. *Normal* | Recovered after transfusions |
| Jakesch cited by v. Gierke | 1-5. Normal<br>6. Hydrops | Placenta 3 times as heavy as normal |
| | 7. *Normal* | |
| King | 1, 2, 3. Normal<br>4. Died third day of jaundice<br>5. Eight months macerated fetus<br>6, 7. Miscarriages at 4 months<br>8. *Normal and well*<br>9. Died eighth day jaundice and convulsions<br>10. Macerated fetus<br>11. Hydrops<br>12. Macerated fetus | |

TABLE II—CONT'D

| AUTHOR | ORDER OF BIRTH | REMARKS |
|---|---|---|
| Lockwood | 1. Died at birth, cause unknown<br>2. *Normal*<br>3. Hydrops | Baby was very large, probable case of erythroblastosis |
| Mackay | 1. Normal<br>2. Miscarriage at 5 months<br>3. Died tenth day jaundice<br>4. *Normal*<br>5. *Normal*<br>6. Died 3 weeks jaundice<br>7. Died twenty-seventh day jaundice<br>8. *Normal* | |
| MacWatters<br>cited by King | 1. Hydrops<br>2, 3, 4. *Normal* | |
| Mannheimer | 1. Congenital anemia<br><br>2, 3, 4. *Normal* | Large liver and spleen, 63,800 W.B.C. 24 erythroblasts per 100 W.B.C. |
| Nason | 1, 2. Normal<br>3. Miscarriage<br>4-7. Jaundiced. Died except seventh child who recovered<br><br><br><br><br>8. Died diarrhea<br>9. Stillbirth<br>10, 11. *Normal* | Mother jaundiced also from fourth to eighth pregnancies. History not like that of acholuric jaundice where children are not so ill, and do not usually die in infancy of the disease |
| Pasachoff | 1, 2, 3. Erythroblastosis fetalis | |
| Rautmann | 4. *Normal*<br><br>1. Normal<br>2. Stillbirth, 7 months<br><br>3. Died third week, intestinal catarrh<br>4, 5. *Normal*<br>6. Hydrops | Mother treated during fourth pregnancy, but does not say how<br><br>Probable case of erythroblastosis fetalis |
| Taylor | 1-4. Normal<br><br><br><br>5. Miscarriage<br>6, 7, 8. Died in few days of jaundice<br>9. *Premature but healthy and survived*<br>10. Died seventh day of jaundice | Several of mother's sisters died in infancy of jaundice and convulsions. May be thought to be acholuric, but in such families infant death and convulsions rare |

TABLE III. FAMILIES IN WHICH ONE TWIN HAD ERYTHROBLASTOSIS FETALIS, OTHER NORMAL

| AUTHOR | HISTORY | REMARKS |
|---|---|---|
| Andrews | 1, 2, 3, 4. Normal<br>5. Eight months fetus<br>6. Twins.  Normal female.  Hydropic male | Both twins died, one at birth, the other 4 hours later. Question as to whether female twin was also affected, but its placenta was normal, while that of hydropic twin was "enormous" |
| Bushnell and Aldrich | 1. Normal<br>2. Died eleventh day, enlarged thymus<br>3. Full-term stillbirth<br>4, 5. Spontaneous miscarriages<br>6. Twins, fraternal.  Female affected.  Other normal | Jaundice at 2 days, transfused many times, lived. Developed cerebral symptoms at 6 mo. Died at 13 months |
| Lynch | 1. Normal but died in few hours<br>2. Twins, said to be monovular because placenta was "single." One normal female, one hydropic female | Liver of affected twin showed "round cell infiltration" (probably hemopoietic areas with many early forms). Also brown bile pigment clumps in cells |
| Oberndorfer cited by Peters | Twins.  One wholly normal.  One hydrops | |
| Wooley | Twins.  One normal.  One hydrops | Delay in birth of normal twin caused by prolonged delivery of hydropic twin caused death of normal infant. No autopsy on normal twin, therefore latent erythroblastosis not excluded |
| Capon | 1. Miscarriage at third month<br>2. Stillbirth<br>3. Twins.  Normal female.  Hydropic female | Both died, organs of normal twin much heavier than normal and would suggest that although outwardly normal, this twin was also a case of erythroblastosis fetalis |

Families in which normal infants are interspersed between miscarriages and stillbirths before they finally end in the production of an hydropic infant are also included here because of the fact that these products of conception are regarded as evidences of the disease. There is evidence then, that Darrow's interpretation does not fit all the cases.

Other observations, not in agreement with Darrow's views, are as follows: She points out that Hampson's use of repeated small doses of the mother's serum in effecting a cure in these children might be regarded as a desensitization process, but Greenwald states that the experience of others does not confirm Hampson's work. Moreover some

of the best results obtained with these children have been secured by transfusions with the mother's whole blood (Diamond, Blackfan and Baty). This work makes one query why giving mother's blood which supposedly has the hemolyzing factor for the infant's hemoglobin in it, should stop the hemolysis and allow the child to recover; also why the condition should progress rather than regress once the child is born, unless in some cases the placenta is impermeable, while the breast secretes the antibodies.

More research is needed on this problem, and one of the contributions must be the determination of the normal development of the hemopoietic system at all stages of fetal life, and the determination of how early the excess hemopoiesis may be detected in cases of miscarriages in families whose earlier history has suggested the probability of erythroblastosis fetalis. Darrow's ideas as to the sensitization of the mother to fetal hemoglobin should be further investigated. When we have a more accurate estimate as to the frequency of this condition, and how often so-called "premature" infants die, not of prematurity but of erythroblastosis, we may judge more adequately the truth of the statements that maternal age plays a role in the etiology of this condition, and that the affected children tend to come at the end of the childbearing period. How many infants with this condition have died who were born in the early years of the mother's obstetric history, and who were not diagnosed properly because the fetus was not examined, we do not yet know.

### SUMMARY

Two and possibly three cases of erythroblastosis fetalis are described. They were the only outwardly normal full-term or near full-term infants received in the embryology laboratory, and two of the three were found to be cases of erythroblastosis fetalis when examined at autopsy, although the infants had been regarded as normal by the obstetrician. It is suggested that this condition may be a cause of many stillbirths at or near term, and of many deaths formerly attributed to prematurity and it may go unrecognized because it does not always cause external manifestations, such as hydrops or jaundice. The obstetrician may receive blame for mismanagement of the case because of the death of the infant. The lives of some of these children might be saved by induction of labor while the fetus is still viable, followed by transfusion, if the obstetrician is aware that the mother has given birth to other offspring with erythroblastosis. Such knowledge will be gained only by subjecting all stillbirths, premature infants and outwardly normal full-term infants, dying immediately after birth, to routine pathologic inspection. Just as "senility" has given way to a more adequate classification in most cases, so "stillbirths" and "prematurity" will give way to more accurate cataloguing as the causes of death are more scientifically determined.

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# THE UNSTRIATED MUSCLE FIBER OF THE FEMALE PELVIS

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THE problem of the mechanics of the uterine supports has attracted the attention of investigators for the past century. The early workers devoted themselves to the anatomy of the "ligamentous supports of the uterus." They assumed that the uterine ligaments were in purely fibrous structures, and it was not until 1888, when Ziegenspeck and Winckel demonstrated the presence of smooth muscle in the base of the broad ligament, that a possible muscular support for the uterus, other than that provided by the levator ani, was conceived.

Since 1891 many workers have drawn attention to the fascial constituents of the pelvic floor and the relation of these to the blood vessels and nerves.

Mackenrodt (1895), summarizing previous work on the constituents of the tissue at the base of the broad ligament and adding his own observations, concluded that smooth muscle fibers extending laterally from the cervix uteri are found constantly in this region. Tweedy (1911 to 1916) considered that these fibers are attached laterally to the endopelvic fascia along the "white line." It is interesting to note that Thompson (1901) attributed the "white line" to a "condition of strain." It is possible that this strain is provided by the pull of these fibromuscular bands. Moritz (1913) denied the existence of separate "ligaments of Mackenrodt" but maintained that they were simply "pelvic areolar tissue" strengthened by perivascular sheaths. He admitted, however, that smooth muscle surrounded the vessels and nerves which form the vascular pedicle of the uterus. It is not a matter of great moment whether the smooth muscle of the pelvis is associated with vessels and

nerves, or whether it is an independent sheet, provided it is admitted that there are such muscular fasciculi attached to the cervix. The uterosacral and round ligaments have long been shown to contain masses of smooth muscle.

Smooth muscle originating in the uterus passes into the uterosacral ligaments. The round ligaments are largely muscular, though receiving considerable connective tissue support from the attached peritoneum. Bovee regarded them as having a strong influence in maintaining the uterus in a forward position. According to Nyulasy (1921), the cardinal ligaments or ligaments of Mackenrodt consist of three fibromuscular ''heads.'' The superior ''head'' is associated with the transverse; the middle ''head'' with the ascending part of the uterine artery; while the inferior ''head'' arises from the lateral vaginal fornix. The three ''heads'' are then inserted into the posterior layer of the broad ligament. He notes that the three ''heads'' are best seen at full-term pregnancy. Smaller bands of smooth muscle have been recognized in the rectovesical and vesicovaginal septa. Goff (1931) described the areolar connective tissue in the rectovaginal and in the vesicovaginal septa, and disclosed its smooth muscle content. His sections taken at various levels were from a well-developed nullipara. Testu (1902) showed that the round ligament is composed of smooth muscle rich in elastic tissue.

The literature upon the fascial supports of the uterus deals chiefly with the surgical aspects. In most of these references there is a considerable lack of precision in the descriptions of the anatomy of the parametrium and of its constituents. In order to obtain accurate observations of the actual origin and insertion of all these ''bands,'' ''fasciculi,'' ''heads,'' and ''ligaments,'' serial sections were prepared of fetal female pelves cut in transverse and sagittal planes. By tracing the course of these muscular tissues which converge upon the uterine cervix, it was possible to reconstruct the whole of this ''smooth muscle diaphragm'' and to formulate some of its functions.

The first part of this paper contains a summary of the observations which have been made. In the discussion which follows the functional aspect and the surgical anatomy of the smooth muscle tissue are described. Materials and Technique: The material consisted of transverse sections of 1 six and 1 seven months' fetus, and of sagittal sections of a seven and one-half months' fetus; and dissections of the pelvis of one full-term fetus; 10 adult pelves and 1 *Macacus rhesus* pelvis. The specimens were prepared by the injection of the abdominal aorta with 10 per cent formalin. After allowing twenty-four to forty-eight hours for hardening. the pelvic contents were removed in a solid block complete with the levator ani and obturator internus muscles. The blocks were embedded in paraffin and sectioned at either 10 or 15 microns. The slides were stained with Ehrlich's hematoxylin and counterstained by the Van Gieson method. Numerous serial drawings were made and prepared on glass slides, but owing to the minute size of some of the muscular bands, these proved to be difficult to interpret, and consequently are not referred to in this text. It was only by tracing individual bundles through the series and by comparing the transverse and sagittal sections that an accurate picture was obtained. The reconstruction of the muscular bands was done schematically in the several drawings, reproduced here, but the course of each fascicle of

muscle tissue is demonstrated by photomicrographs of the actual sections taken at a uniform magnification of 16.8 diameters except in Fig. 7, where the magnification was 6 diameters.

### OBSERVATIONS

The smooth muscle tissue, lying between the pelvic peritoneum and the upper or superior surface of the levator ani muscle, is arranged as a series of bundles radiating from the uterus at the level of the internal os. The peripheral attachments of these bundles enable the tissue to be divided into three groups of fibers: anterior, lateral, and posterior groups.
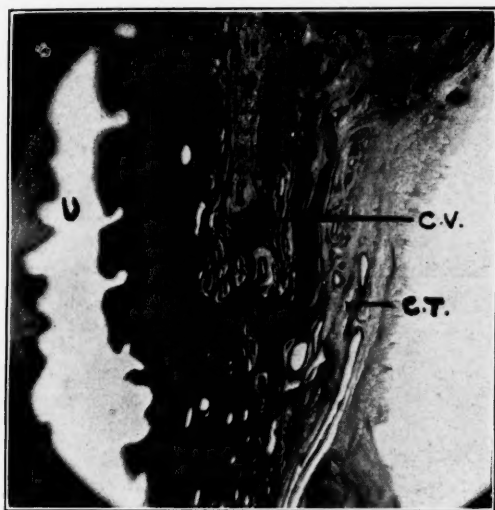


Fig. 1.

Fig. 2.

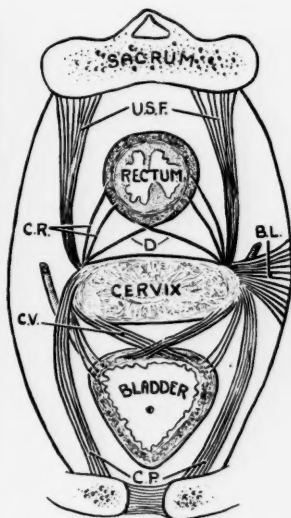Fig. 1.—*U.*, uterus; *C.V.*, cervicovesical fibers; *C.T.*, connective tissue.

Fig. 2.—*C.P.*, cervicopubic bundle; *C.V.*, cervicovesical fibers (decussating); *C.R.*, cervicorectal fibers; *D.*, decussation; *B.L.*, broad ligament (lower bundle); *U.S.F.*, uterosacral fibers.

The *anterior fibers* arise from the anterior and the anterolateral aspect of the cervix and are attached (a) to the posterior aspect of the os pubis either directly or through the intermediary of fibrous bands and (b) into the muscular coat of the bladder. The muscle fibers which make up this group can be subdivided into the following bundles:

a. *The cervicovesical bundles:* (Figs. 1 and 3). These pass as a thick bundle of fibers from the cervix at the level of the internal os, converge toward the median sagittal plane, and intermingle with the circular and longitudinal coats of the bladder musculature. They terminate at the base of the bladder in the trigonal muscle. Beneath these muscular fibers is a connective tissue stratum directed toward the os pubis. Between these two structures numerous veins are seen. In the fetus, the bladder and pelvic viscera being abdominal organs, the upward obliquity of the smooth muscle fibers is very pronounced.

b. *The cervicopubic bundle:* (Figs. 1 and 2). From the level of the internal os passing upward toward the posterior surface of the os pubis, there pass many bundles of muscle tissue which are longer than the cervicovesical masses. They pass alongside of and beneath the base of the bladder and end either directly on the os pubis

or insert themselves into the fascia covering the bone. Beneath this bundle lies a layer of connective tissue which radiates from the cervix to the posterior surface of the os pubis. This is the same layer that was described in relation to the cervico-vesical bundles.
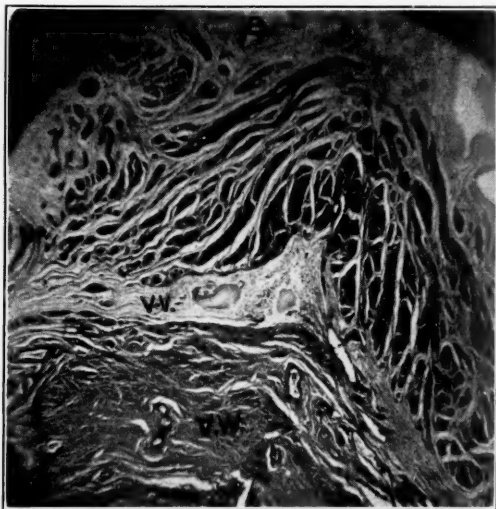


Fig. 3.—*B.*, bladder; *U.R.*, ureter; *V.V.*, vesicovaginal septum; *V.W.*, vaginal wall.



Fig. 4.—*V.*, vagina; *A.F.*, anterior fornix; *C.V.*, cervicovaginal fibers.

c. *The vesicovaginal bundle:* (Figs. 2, 3 and 10). In the vesicovaginal septum, smooth muscle fibers pass medially from the lateral vesicovaginal junction into the vesicovaginal septum, where they decussate. Near the junction of the posterior wall of the urethra and the anterior vaginal wall they are quite pronounced. At a lower level where the base of the bladder is in contact with the vaginal wall, these fibers are less numerous, and a loose avascular areolar connective tissue stratum is present (Fig. 3). At the lateral vesicovaginal junction condensations of smooth muscle are present in whose meshes nerve ganglia and vessels are seen.

d. *The cervicovaginal bundle:*  (Fig. 4).   Short fibers pass from the cervix slightly below the level of the internal os and pass to the musculature of the anterior vaginal fornix.
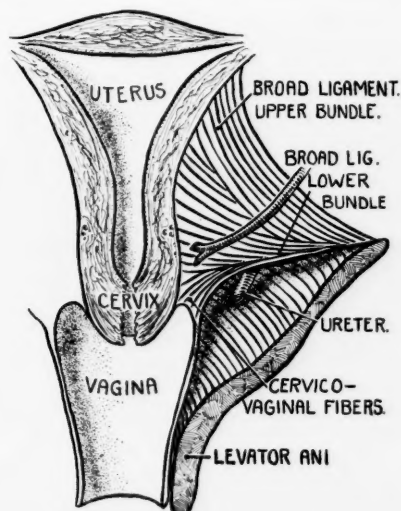


Fig. 5.—Schematic representation of smooth muscle fibers in the broad ligament representing upper bundle, lower bundle, and cervicovaginal fibers.



Fig. 6.—*U.S.F.,* uterosacral fibers;  *U.R.,* ureter;  *U.A.,* uterine artery.

*The Lateral Group.*—The lateral group (which is apparently identical with the ligaments of Mackenrodt) arises similarly from the lateral aspect of the cervix. They diverge and form a flattened fan of fibers which is attached by means of fibrous strands to the ''arcus tendineus.'' This group is subdivided into an upper and lower bundle.

a. *The upper bundle:*  (Fig. 5).  The fibers which make up this bundle are short and radiate from the upper lateral uterine wall. They pass in an oblique and caudal direction, terminating in the subperitoneal connective tissue.

b. *The lower bundle:* (Figs. 3 and 5). These fibers originate slightly above the level of the internal os, and course in a lateral direction to terminate at the "arcus tendineus." This bundle of fibers contains the transverse portion of the uterine artery and passes above the ureter. Many nerve ganglia belonging to the inferior hypogastric plexus are surrounded by its fibers. From slightly below the level of the internal os fibers pass to the lateral vaginal fornix. Beneath the lower bundle



Fig. 7.—Rectal fibers and rectovaginal septal fibers. *C.R.*, cervicorectal fibers.
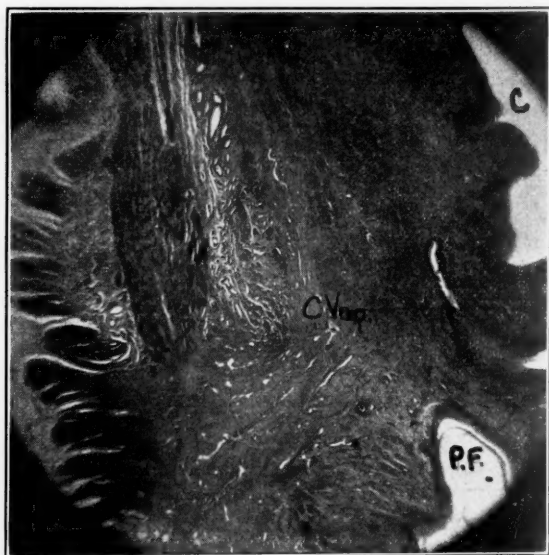


Fig. 8.—Posterior vaginal fornix fibers. *P.F.*, posterior fornix; *C.*, cervix; *C.Vag.*, cervicovaginal fibers.

there is a stratum of areolar connective tissue, radiating from the cervix to the "white line" and to the superior layer of fascia of the levator ani muscle. In the upper medial part of this areolar connective tissue, lateral to the vaginal fornix, the ureter passes on its way to the bladder.

*The Posterior Group.*—(Fig. 2.) Also arising from the cervix enter into the composition of the uterosacral ligaments or find insertion into the rectal walls, and rectovaginal septum.

a. *Uterosacral fibers:* From the posterior-lateral aspect of the cervix, these at the level of the internal os, fibers pass posterolaterally beneath the peritoneum which forms the superior lateral boundary of the pouch of Douglas, and these fibers are lost in the presacral fascia over the second and third sacral vertebrae. Many nerve ganglia are present among their fibers. Figs. 2 and 6 show early smooth muscle fibers entering the parenchymatous uterosacral ligament (6 months' fetus).

b. *Rectal fibers:* (Figs. 2 and 7). These fibers sweep downwards and medially from the posterolateral aspect of the cervix and passing about the upper posterolateral wall of the vagina, swing into the rectum in its anteromedial area, where they are lost in its circular and longitudinal coats.

c. *Posterior vaginal fornix fibers:* (Fig. 8). From the posterolateral aspect of the cervix slightly below the internal os, short fibers pass to the musculature of the posterior vaginal fornix.

d. *Rectovaginal septum fibers:* (Figs. 2 and 7). Fibers sweep in from the rectovaginal junction, passing between the posterior vaginal wall and anterior rectal wall, where they decussate and are lost on the walls of these structures.

Besides these distinctive strands enumerated above, short fibers enter the anterior and posterior peritoneal layers of the broad ligament, from the corresponding uterine surfaces, and end deep in the endothelium.

### DISCUSSION

During the last three months of fetal life, smooth muscle tissue exists in definite masses in the subperitoneal pelvic space. The arrangement of the tissue is identical with that in the adult, except that it is much less massive and the direction of the bands varies owing to the difference between the positions of the pelvic organs in fetal and adult life. The smooth muscle tissue is not confined only to the areas immediately surrounding blood vessels and nerves. Most of it is made up of strands entirely independent of these structures. When they are reconstructed and viewed from the superior aspect, the direction of the fibers leads one to consider the tissue as an imperfect "diaphragm" of smooth muscle converging on the uterine cervix. It is true that there are other parts of the tissue which do not enter into the formation of this "diaphragm" but are seen as independent masses of muscle tissue, or as continuations upward of the lateral ligaments (of Mackenrodt) on to the lateral edges of the uterus. The round ligament is, of course, entirely independent. The observations recorded above raise some interesting problems: (a) The origin of the muscle cells; (b) the function of the muscle tissue in the adult.

The first problem cannot be solved from the material at my disposal. In a six months' fetus, e.g. (Fig. 6), it has been possible to make out masses of undifferentiated cells lying in areas corresponding closely to those in which smooth muscle tissue becomes apparent at a later date. These cells are in all probability primitive myoblasts, but it is not possible to be certain whether they are migrating cells from the smooth muscle walls of the Müllerian ducts, or are spe-

cializations in situ of the mesenchymatous cells within the urogenital septum. It is quite clear, however, that the tissue is not derived from the musculature of the blood vessels, as many of the anlagen of the strands are entirely separate from any vessels possessing a muscular coat. Further study is necessary to clear up this question. With regard to the function of these fibers, it is obvious that no direct evidence can be presented. Two sources of knowledge provide relevant facts: (a) the anatomic arrangement of the fibers, and (b) the surgical procedures and observations which have been undertaken to repair or reconstruct the pelvic floor in cases of prolapse and traumatism.

The distribution of the smooth muscle is interpreted diagrammatically in Figs. 2 and 5. Its arrangement, as has been pointed out above, is in the main slinglike. Considered generally, it forms an imperfect diaphragm within the connective tissue that forms the substance of the various pelvic ligaments. This smooth muscle sling is insufficient in strength to support the pelvic viscera. There is a striking similarity between the bundles of the pelvic unstriped muscles and the component muscles of the levator. The fan-shaped ligaments of Mackenrodt resemble in direction, if not in extent, the iliococcygeus and some of the pubococcygeus fibers, and the pubocervical and the cervicovesical fibers have striking counterparts in the subdivision of the pubococcygeus, which is more properly called the sphincter vaginae.

If the muscle tissue cannot be considered a diaphragm except so far as its defects are made whole by fascia, it may have other functions according to the arrangement of its several parts. Fascia, in itself, is not unusually found in regions subjected to intermittent and varying degrees of tension. Usually it is most developed where it can respond as a passive elastic agent which must be extended beyond its quantum of elasticity. Smooth or striated muscle, however, having the property of maintaining "tension" or "tonus," can withstand extension or stretching, which could not be tolerated by mere fascia. If, however, owing to nutritional or mechanical factors, its power of maintaining a high tonus is lessened, then it is a much less efficient supporting structure than is fascia. Smooth muscle has the property of maintaining, within fairly narrow limits, the same tonic force irrespective of the degree of stretch to which it is subjected until the limit of its elasticity is reached. From then on it behaves as an inactive fascial tissue. These considerations, when applied to the arrangements of the tissue as described above, are of fundamental importance. The muscle tissue is found precisely in those regions where it is necessary to permit considerable dilatation, contraction, or movement of organs, meanwhile maintaining some degree of control of the movements of these organs independently and in relation to each other.

It is obvious that it is necessary to have a mechanism to restore the normal state after a major dilatation, etc., of one or more of the organs. It is equally obvious that fascia would be ineffective in such contingencies. Viewing now the smooth muscle in terms of actual mechanism, the following principal arrangements can be recognized: (a) The mechanism for fixation of the cervix uteri; (b) the mecha-

nism of sphincteric arrangement; (c) the mechanism of special fiber units.

a. *The mechanism for fixation of the cervix uteri:* The human uterus lies in the physiologic position of anteflexion and anteversion. The body of the uterus lies in the direction of the axis of the pelvic inlet, with the fundus directed upward and forward, and the cervix pointing downward and backward. Because of the strategic attachment of its fibers the extravisceral smooth musculature plays an important role in maintaining the uterus in its normal position. The three groups of fibers, anterior, lateral, and posterior, radiating from the uterus to their insertions, help to maintain the cervix at a fixed level and in the direction of the axis of the pelvis. The anterior group, when contracting, make taut the posterior group fibers; they are its tensors and antagonists; conversely, the posterior group are the antagonists of the anterior group fibers. Nevertheless, when both groups are contracting under equal tension, they unite in a synchronous effort to promote fixation. The lateral fibers in the broad ligament as a group are attached slightly anterior to the central axis of the uterus, and help to maintain the uterine body anterior to the axis of the pelvis. The upper fibers of this group being inserted into the subperitoneal connective tissue, help to hold the uterus suspended on the connective tissue scaffolding. The lower fibers because of their insertion into the arcus tendineus, unite with the upper fibers in suspending the area of the internal os at a fixed level. The posterior fibers are the auxiliaries of the round ligaments.

The round ligaments, in association with the upper portion of the broad ligaments in a coronal plane, are fixed anterior to the midline of the uterus, and thus help to maintain the anteflexion and anteversion of this organ. The maintenance of anteflexion and anteversion is also assisted by the downward intra-abdominal pressure. The uterus and the broad ligaments constitute the deflecting plane. The uterus is pressed against the posterosuperior surface of the bladder, which in turn rests upon the cervicopubic ligaments, thus making them tense, while at the same time tension will be more or less passed on to the lateral and posterior portions of the smooth muscle diaphragmatic sling. A uterus in malposition, such as in retroversion and retroflexion, will have this condition accentuated by the continued force of intra-abdominal pressure. The smooth muscle diaphragm in its posterior portion will have tension exerted upon it, the uterosacral ligaments will soon become elongated and their elasticity lost. The equilibrium between the anterior and posterior fiber groups will ultimately be destroyed, and the malposition will be further accentuated, and eventually will result in a descensus uteri. The fascial structures with which this smooth musculature is associated are also of importance in determining uterine position. Beneath the smooth muscle diaphragm is a stratum of connective tissue, following very much the same general outline as the smooth muscle. Its fibers converge medially to their insertion at the cervix. The tissue also forms considerable deposits of connective tissue around the pelvic viscera, especially at the vaginal fornices.

b. *The mechanism of sphincteric arrangement:* Smooth muscle fibers in the lateral pelvic gutters, in the anteroposterior plane above the vaginal fornices, and between the bladder and cervix, and cervix and rectum, have a sphincteric arrangement (Fig. 9). The boundaries of this lateral pelvic gutter are, laterally, the converging fibers of the levator ani muscle and the arcus tendineus; to the medial side lie the lateral and posterolateral borders of the base of the bladder; the vesicovaginal junction; the lateral vaginal fornix; the rectovaginal junction, and the lateral rectal wall. In this plane, smooth muscle fibers encircle the base of the bladder, the vaginal fornices, and the rectum (Fig. 9).

At the lateral vesicovaginal junction, condensations of smooth muscle exist, in whose meshes are nerve ganglia and vessels. From this vesicovaginal junction, smooth muscle fibers proceed in a circular direction about the upper anterior vaginal fornix, to meet fibers from the corresponding areas of the opposite side, i.e., decussating fibers in vesicovaginal septum (Fig. 9). At the rectovaginal junction an analogous arrangement is present, i.e., the fibers decussate in the rectovaginal septum (Fig. 7). Nerve ganglia are present in greater numbers in this area. The distribu-

tion of the fibers is such as to imply a sphincteric function. Physiologically the marked changes both in size and configuration that the pelvic viscera frequently undergo, necessitate some compensating mechanism in the surrounding tissue.

Dilatation of the connective tissue diaphragm, to the extent of permitting the passage of the fetal head, demands a great stretching of this poorly contractile tissue, which of itself could not assume its original dimensions as it contains little, if any, elastic tissue. The return to the normal post-partum state is assisted by the closely associated smooth muscle diaphragm which has the power of greater extensibility. The fibromuscular diaphragm is not necessarily injured in normal childbirth. Dilatation of the uterus and cervical canal will slacken the tautness of the fibromuscular diaphragm, while return to the normal size of this viscus will renew the tension of the musculofascial diaphragm.
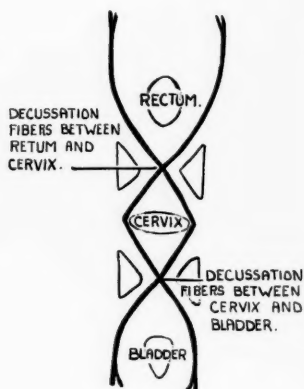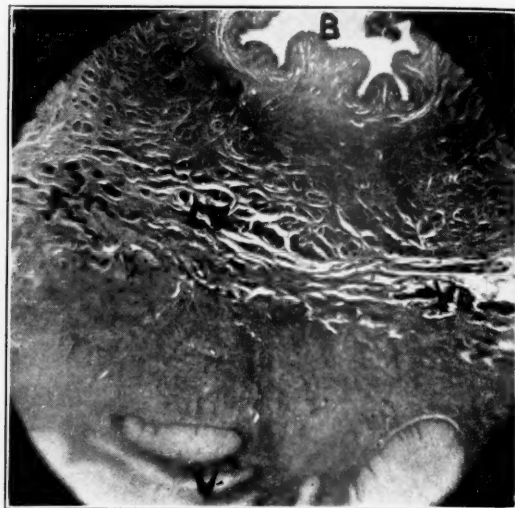


Fig. 9.



Fig. 10.

Fig. 9.—Decussation fibers.
Fig. 10.—Vesicovaginal septum. *B.*, bladder; *C.V.*, cervicovesical septum; *V.*, vagina.

*c. Consideration of special fiber units:* (1) The cervicovesical fibers of the smooth muscle diaphragmatic sheet, which terminate in the trigonal muscle, may possibly be associated with the mechanism of micturition. The lower part of the vesical sphincter and the posterior urethral floor are associated with the longitudinal fibers of the muscle of the bladder trigone. The smooth muscle fibers which run forward and upward from the lateral vesicovaginal junction into the bladder musculature, terminate at the area of the trigone. It is possible that tension on these fibers will tend to pull on the trigonal muscle and help to open the vesical sphincter in its lower half. (2) The cervicopubic fibers: The bladder sits on a musculofascial platform, the upper part of the bladder wall is distensible, but the lower part is more fixed; this is the area of the trigone. The base of the bladder may make limited excursions in a craniocaudal, or a lateral, or an anteroposterior plane. This range of movement is facilitated by the smooth muscle content in its musculofascial floor. Deficiencies in the smooth muscle cervicopubic sheet are productive of cystocele. Should this muscular sheet be deficient, the strain will be thrown immediately on the fascial supports, which cannot well sustain continued strain, and will eventually give way at the weakest point. If the attachment of the cervicopubic sheet to the os pubis yields, the bladder and urethra will slide down behind the symphysis pubis. If the deficiency occurs in the middle part, the base of the bladder protrudes through its

herniated edges. Later the fascia yields and a cystocele develops. If the sheet yields at its cervical origin, the anterior vaginal fornix prolapses, and an associated cystocele appears, its size and position depending on the area of weakening of the cervicopubic sheet.

*The Lateral Group.*—a. Upper fibers arising from the lateral uterine wall do not reach the arcus tendineus but terminate in the subperitoneal connective tissue of the broad ligament. Other fibers are inserted into its anterior and posterior folds. This latter insertion provides a resilient supporting mechanism to the peritoneal folds of the broad ligament, while the fibers terminating in the subperitoneal connective tissue help to steady the uterus, and their contraction, in conjunction with the lower fibers, would tend to pull up the uterine artery and ureter and to obliterate the lateral vaginal fornices.

b. Lower fibers: The marked condensation of the smooth muscle fibers about the transverse part of the uterine artery, in the region of the internal os, is of great interest. It seems very probable that this large artery, running through an exceptionally loose tissue, may need such support as this smooth muscle would provide to help maintain its tone. If this is so, it would be a point of great importance in regard to the frequent occurrence of excessively dilated vessels in this area.

c. Cervicovaginal fibers from the lower group help to give support to the lateral and anterior fornices.

*The Posterior Group.*—a. Uterosacral fibers: These complete the posterior elements of the smooth muscle diaphragm, and draw the cervix backward and upward toward the sacrum. They are the tensors of the vesicovaginal septum. They help support the cervix at a fixed level.

b. Cervicorectal fibers pass as fixation bands into the muscle wall of the rectum. They are possibly supportive and prevent prolapse of the mucous membrane.

c. Cervicovaginal fibers act in a similar way to those fibers in the anterior and lateral fornices.

d. Rectovaginal septal fibers: They have been considered under septal fibers in discussing the possible sphincteric control of the smooth musculature.

### RELATION TO THE RATIONALE OF CERTAIN SURGICAL PROCEDURES

In the foregoing discussion the suggested function of the several parts of the smooth muscle tissue has been approached upon purely structural grounds. Surgery attempts to repair the results of damage to the pelvic outlet caused by childbirth. The procedures which have been devised are numerous, a sure indication that most of the operations are ineffective. An analysis of the literature of operations for the cure of rectocele, cystocele, and descensus uteri, has revealed the fact that the smooth muscle bands within the subperitoneal pelvic tissue have been consistently ignored or their existence not realized by many surgeons who have invented new methods of restoration. It is not extraordinary, therefore, that one should find that the most successful of the repair operations are those whose authors have consciously or unconsciously realized the importance of using certain "fasciae" which, in reality, are mainly smooth muscle. Basing his conclusions on anatomic data, Fothergill, in 1907, clearly established that the smooth muscle and connective tissue attached to the sides of the cervix and vagina are the important combinations which hold the bladder, uterus and vagina in position. He concluded that the disturbance of these musculofascial planes permitted a hernia of the pelvic viscera, through their weakened lines of support, and that restoration to normal lines of the disturbed planes would cure the

hernia. With this premise, he devised the operative procedure of denuding the vaginal mucosa and separating along the avascular line of cleavage between the vagina and bladder (Fig. 3) and performing "fascial lapping" of the vesicovaginal and rectovaginal septa. Later he added cervical amputation to his original operation. This "fascial lapping" reduced the operative risk very much, and obviated the necessity of abdominal section. An analysis of his operative technique shows that in his plication of the vesicovaginal and rectovaginal septa, he sutured the smooth muscle fibers of the anterior and posterior groups, under the impression that he was merely effecting reposition of the deposed lines of fascia through which the viscera had protruded. However, by this maneuver the smooth muscle planes are restored to their normal relationships, thus enabling this tissue to exert its active function in providing pelvic support.

From the date of Fothergill's epoch-making research in anatomy and surgery, numerous modifications have been added to the operative technique for the cure of prolapse. When these various modifications are examined critically, it is found that while fascial repair is often very greatly emphasized, the successful procedures can be shown to depend upon whether or not the smooth muscle groups of the fascia are utilized. Thus Fitzgibbons, in 1916, and Chipman, in 1918, both described their technique for he repair of the fascial sling. These modifications, irrespective of abdominal procedures, were differences in operative technique, rather than actual fundamental operative procedures. In the final analysis, both operators performed "fascial lapping" of the septa. They took out the slack of the vesicovaginal and rectovaginal septa by coaptation of its herniated edges, thus at the same time performing the identical maneuver in the anterior and posterior group fibers of the smooth muscle sling. Many others have added their modifications of greater or lesser degrees.

The procedure in all these operations shortens and reinforces the cervicopubic fiber groups in front; the lateral fiber group laterally; and the uterosacral group posteriorly. In the same way, other variations of operative technique have been described, and in each case those which have been proved successful make use of the smooth muscle groups. The emphasis has usually been placed merely on fascial repair, but we must now come to a realization of the fact that the essential factor in successful repair operations, as well as in the normal functioning of the supportive mechanism, is the smooth muscle content of the fascia rather than the fascia itself.

### SUMMARY

An imperfect smooth muscle diaphragm is present and embedded in fibrous tissue, lying between the pelvic peritoneum and the superior surface of the levator ani muscle. The bands which constitute this diaphragm may be divided into anterior, lateral, and posterior groups, converging on the cervix uteri. The attachments of these to the visceral and pelvic walls, and their function, are discussed in terms

of the individual bands and the musculature as a whole. Operative procedures for the correction of sacropubic hernia are criticized, and their success or failure interpreted in the light of the dual nature of both parametrium and pelvic subperitoneal tissue.

1610 SHERBROOKE STREET WEST

# CIRCULATION TIME STUDIES IN PREGNANT WOMEN WITH RHEUMATIC HEART DISEASE

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THE investigation of circulatory changes in the pregnant woman has recently been undertaken in detail by various clinics. However, similar studies in the pregnant woman with a cardiac lesion have not yet been reported.

In normal pregnancy the following observations have been made on circulation and related aspects of the circulation.

Lindhard,[1] Stander and Cadden,[2] Haupt,[3] Schmidt,[4] Schroeder,[5] Anthony and Hansen[6] have shown that the minute volume output of the heart increases, from a minimum of 15 per cent to a maximum of 74 per cent, from the fourth month of gestation onward.

Dieckmann and Wegner,[7] Schoenholz,[8] and others have shown an increase in plasma, a relative or absolute diminution in the number of formed elements, and a relative anemia.

Vital capacity remained constant or rose slightly during the course of pregnancy in the majority of patients according to Thomson and Cohen.[9] Alward[10] reported a gradual reduction of the vital capacity in the last month of pregnancy.

Gammeltoft[11] and Corwin, Herrick, Valentine and Wilson[12] showed that there was a progressive elevation of the pulse rate during pregnancy.

Greenstein and Clahr[13] concluded that by means of circulation studies, it is possible to demonstrate a slight but progressive retardation of blood flow in the course of pregnancy.

We have made circulation studies on a group of pregnant women with definite cardiac involvement. Our purposes were first, an endeavor to correlate the functional classification of the patient, based on subjective data, with the more objective method of circulation time; and second, to determine the value of circulation time tests in predicting the onset of cardiac failure in pregnancy.

The mortality from heart disease complicating pregnancy gathered from various clinics by Jensen[14] varies from 4.8 per cent to 28 per cent of all maternal deaths. The methods of lowering this mortality from cardiac failure in pregnancy are particularly effective if the condition is recognized early enough.

## PROCEDURE

Nineteen pregnant women with rheumatic heart disease were selected from the Prenatal Clinic of the Morrisania City Hospital. If any other complication existed the woman was rejected for this investigation. The patients were instructed to return to the clinic every two weeks for physical examination and determination of their functional classification according to the criteria of the New York Heart Association, and every four weeks for circulation time rates. Incomplete records were due to lack of cooperation of the patient or late registration at the clinic. If the patient was hospitalized, readings were taken more often. Every patient had at least one electrocardiogram and one fluoroscopic examination during the gestation. The history and physical examination of each patient were recorded in the special form prescribed by the American Heart Association.

There were 23 pregnancies in the group of 19 women. Two of the pregnancies were terminated at a different institution.

## METHODS

The arm-tongue time was measured according to the procedure of Fishberg, Hitzig and King.[15] With the patient at rest for fifteen to twenty minutes, 3 c.c. of a concentrated solution of saccharin were injected rapidly into the antecubital vein through an 18 gauge needle. The patient was instructed to announce when a sweet taste was first detected at the base of the tongue. Timing was begun from the first drop injected. This is the arm-tongue time and measures the passage of blood through the right and left sides of the heart.

With the needle in situ, the syringe was removed and replaced by one containing 3 c.c. of a 10 per cent ether solution in sterile distilled water. The patient was instructed to exhale forcefully, and the solution was injected rapidly. The time was measured by means of a stop watch from the beginning of the injection until the moment the examiner detected the odor of ether. This measures the arm-lung time[16] or the passage of blood through the right heart as far as the arterial capillaries of the lung.

Of the 19 cases studied, 16 women had mitral stenosis and insufficiency, one had mitral stenosis, one had mitral insufficiency, and one had mitral stenosis and insufficiency and aortic stenosis and insufficiency. Two of the patients who originally showed mitral stenosis and insufficiency developed aortic insufficiency during the subsequent pregnancies. Seven were primiparas and the remaining 12 multiparas. Twelve of these patients remained in a compensated state (Class 1 or 2a) throughout the entire pregnancy and 7 patients at some time gave symptoms or signs of cardiac insufficiency (Class 2b or 3).

*Arm-Tongue Circulation.*—There were 55 determinations of arm-tongue time done on the 19 patients. Table I demonstrates the fact that the arm-tongue time varied from month to month but did not show a constant increase or decrease as gestation progressed.

Forty-eight determinations were made when the patients did not show any signs or symptoms of cardiac insufficiency (1 or 2a). The minimum time was 7.2 seconds and the maximum time sixteen seconds (represented by black dots in Fig. 1). The normal range in nonpregnant women is eight to sixteen seconds[15] and in normal pregnant women from eight to 15.8 seconds.[13]

The remaining 7 determinations of arm-tongue time were obtained from 5 women who were in Class 2b (presented signs or symptoms of cardiac insufficiency). The circulation rates were 18, 17.4, 17.8, 20, 20, 20 and 20 seconds (represented by black circles in Fig. 1).

*Arm-Lung Circulation.*—Arm-lung circulation was determined 51 times on 18 patients (Table I). Here again as in the arm-tongue circulation there were variations in the times without any definite tendency to an increase or decrease as gestation progressed.

Forty-six of the arm-lung determinations were made when the women were completely compensated (Class 1 or 2a). These figures are represented by black dots in Fig. 2. The minimum time was 2.8 seconds and the maximum time 7.1 seconds.

Six arm-lung determinations were obtained when the women had cardiac insuffi-
ciency (Class 2b).    The figures for this group were 4.6, 6.1, 6.2, 6.8, 7.0, and 7.4
seconds (represented by black circles in Fig. 2).

The arm-lung time in normal nonpregnant women is four to eight seconds[15] and
in normal pregnant women 2.5 to 7 seconds.[12]
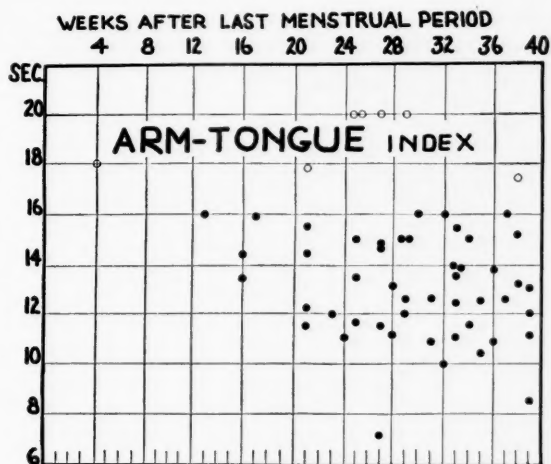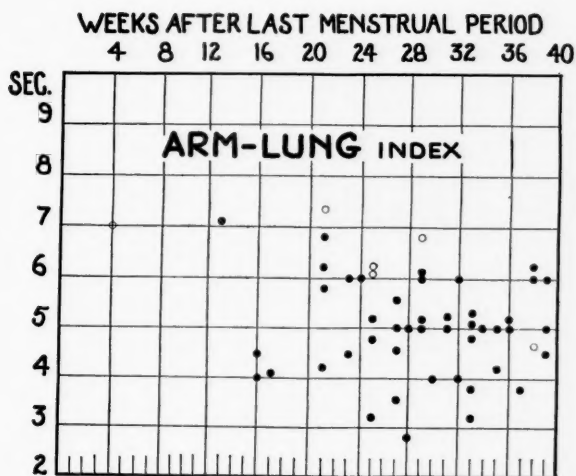


Fig. 1.



Fig. 2.

## DISCUSSION

Blumgart[17] showed that the greatest part of the time required for
the blood to pass from the antecubital vein through the right and
left sides of the heart is consumed in the lung capillaries, the other
components being negligible factors.  In other words, circulation time
really measures the time required for the passage of blood through

TABLE I

| CASE | AGE | PARITY | PERIOD OF GESTATION (WEEKS) | CARDIAC DIAGNOSIS | | | | PULSE RATE | BLOOD PRES. | CIRCULATION TIME | | HISTORY OF DECOMPENSATION | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | ETIOLOGIC | ANATOMIC | PHYSIOLOGIC | FUNCTIONAL CAPACITY | | | ARM-LUNG (SEC.) | ARM-TONGUE (SEC.) | | |
| 1 | 35 | 5 | 33 | Rh. Fev. | MI* MS EH | RSR† | 2a | 112 | 125/ 70 | | 15.4 | No | Spontaneous delivery |
| | | | 37 | | | | 2a | 104 | 140/ 80 | | 16.0 | | |
| 2 | 28 | 2 | 13 | Rh. Fev. | MI MS EH | RSR | 2a | 100 | 120/ 90 | 7.1 | 16.0 | No | Spontaneous delivery anencephalic monster |
| | | | 17 | | | | 2a | 90 | 125/ 70 | 4.1 | 15.9 | | |
| | | | 21 | | | | 2a | 102 | 130/ 80 | 4.2 | 11.4 | | |
| | | | 25 | | | | 2a | 100 | 110/ 70 | 3.2 | 13.4 | | |
| | | | 29 | | | | 2a | 88 | 115/ 70 | 6.1 | 15.0 | | |
| | | | 34 | | | | 2a | 96 | 120/ 80 | | 15.0 | | |
| | | | 38 | | | | 2a | 104 | 130/ 90 | 6.2 | 15.2 | | |
| 3 | 22 | 0 | 25 | ? | MI MS EH | Tachy-cardia | 2b | 132 | 130/ 90 | 6.1 | 20.0 | No | Spontaneous premature delivery, 27th week. Decompensation 2 days antepartum |
| 4 | 26 | 4 | 39 | ? | MI MS EH | RSR | 1 | 104 | 118/ 90 | 6.0 | 11.1 | No | Spontaneous delivery |
| 5 | 20 | 0 | 23 | Rh. Fev. | MI MS EH | RSR | 2a | 96 | 120/ 70 | 6.0 | 7.2 | No | Low forceps |
| | | | 27 | | | | 1 | 100 | 135/ 70 | 4.6 | 12.6 | | |
| | | | 31 | | | | 1 | 100 | 115/ 80 | 5.3 | 12.5 | | |
| | | | 35 | | | | 1 | 104 | 110/ 80 | 5.0 | | | |

| Case | | No. | Age | Etiology | Diagnosis | | Rhythm | Class | HR | BP | CT | CT | Op. | Remarks |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 6 | 29 | 1 | 21 25 29 33 38 39 | Rh. Fev. | MI MS | EH | RSR | 2a 2a 1 2a 2b 2a | 112 92 84 92 76 78 | 90/60 85/50 80/50 80/50 100/70 | 5.8 5.2 5.0 5.1 4.6 | 15.5 11.6 12.6 12.4 17.4 13.0 | No | Spontaneous delivery. Upper resp. infection in 38th wk. |
| 7 | 28 | 5 | 16 | Rh. Fev. | MI MS EH | | RSR | 2a | 80 | 120/70 | 4.5 | 13.4 | No | Spontaneous delivery |
| | 31 | 6 | 4 | | MI MS EH | | RSR | 2b | 96 | 120/80 | 7.0 | 18.0 | No | Vaginal hysterotomy and sterilization |
| 8 | 25 | 0 | 16 25 27 29 30 32 | Rh. | MS EH | | RSR | 2a 2a 1 2a 2a 2a | 84 76 85 84 100 96 | 120/65 110/60 110/60 110/70 110/60 95/50 | 4.0 4.8 3.6 6.0 4.0 6.0 | 14.4 14.6 15.0 16.0 16.0 | No | Decompensation, 29th week. Premature del. 8th mo. Car. failure post partum |
| 9 | 24 | 1 | 21 27 31 35 | Rh. Fev. | MI MS EH | | RSR | 2a 2a 2a 2a | 92 120 120 104 | 110/75 110/60 110/60 120/60 | 6.8 5.6 5.0 4.2 | 12.2 11.4 10.8 10.4 | No | Spontaneous delivery |
| 10 | 33 | 0 | 21 25 27 29 | ? | MI MS EH | | RSR | 2a 2b 2b 2b | 96 90 100 92 | 120/80 100/60 100/65 100/70 | 6.2 6.2 6.8 | 14.4 20.0 20.0 20.0 | No | Premature delivery 8th mo. Decompensation in labor |
| 11 | 28 | 0 | 21 25 | Rh. Fev. | MI MS EH | | RSR | 2b 2a | 120 88 | 120/70 | 7.4 | 17.8 15.0 | No | Decompensation 5th mo. Induction of labor 6th mo. |
| 12 | 19 | 2 | 32 36 | ? | MI EH | | RSR | 2a 2a | 88 104 | 118/62 125/60 | 4.0 5.0 | 10.0 10.8 | No | Spontaneous delivery |

*MI, Mitral insufficiency; MS, mitral stenosis; EH, enlarged heart; AI, aortic insufficiency; AS, aortic stenosis.
†RSR, Regular sinus rhythm.

TABLE I—CONT'D

| CASE | AGE | PARITY | PERIOD OF GESTATION (WEEKS) | ETIOLOGIC | ANATOMIC | PHYSIOLOGIC | FUNCTIONAL CAPACITY | PULSE RATE | BLOOD PRES. | CIRCULATION TIME ARM-LUNG (SEC.) | ARM-TONGUE (SEC.) | HISTORY OF DECOMPENSATION | REMARKS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 22 | 2 | 36 | Rh. Fev. | MI  MS  EH | RSR | 2a | 72 | 105/65 | 5.2 | 13.8 | No | Spontaneous delivery |
| 14 | 18 | 0 | 38 | Rh. Fev. | MI  MS  EH | RSR | 1 | 84 | 130/70 | 6.0 | 13.2 | No | Low forceps |
| 15 | 32 | 1 | 24 28 33 | Rh. Fev. | MI  MS  AI  AS  EH | Tachycardia | 2a 2a 2a | 132 90 80 | 130/42 144/40 145/20 | 6.0 2.8 4.8 | 11.0 11.1 14.0 | No | Class 2b in 5th mo. Decompensation in labor |
| 16 | 22 | 1 | 34 39 | ? | MI  MS  EH | RSR | 2a 2a | 116 100 | 142/90 135/80 | 5.0 5.0 | 11.5 8.5 | No | Spontaneous delivery |
| 17 | 27 | 4 | 27 | Rh. Fev. | MI  MS  EH | RSR | 2a | 108 | 110/60 | 5.0 | 14.8 | No | Spontaneous delivery |
| 18 | 22 | 0 | 39 | Rh. Fev. | MI  MS  EH | RSR | 2a | 80 | 140/100 | 4.5 | 12.0 | No | Low forceps |
|  | 24 | 1 | 23 29 33 37 | | MI  MS  AI  EH | RSR | 2a 2a 1 2a | 84 88 80 100 | 135/75 120/60 128/65 130/60 | 4.5 5.2 3.4 3.8 | 12.0 12.0 11.0 12.6 | | Spontaneous delivery |
| 19 | 27 | 1 | 33 | Rh. Fev. | MI  MS  EH | RSR | 1 | 92 | 120/60 | 3.8 | 13.8 | No | Spontaneous delivery |
|  | 29 | 2 | 28 33 | | MI  MS  AI  EH | RSR | 2a 2a | 120 100 | 138/70 135/60 | 5.0 5.4 | 13.1 13.5 | | Spontaneous delivery |

the lungs, and increase or decrease in time reflects a corresponding alteration in the speed of pulmonary circulation.

In rheumatic heart disease with mitral involvement, failure of the circulation is ushered in by a relative weakening and insufficiency of the left side of the heart. This results in a damming back of blood flowing through the pulmonary bed. Since arm-tongue time is almost wholly a measure of the rate of blood flow through the pulmonary bed, a retardation of flow will give a prolonged arm-tongue time (Blumgart[17]).

The value of circulation time determinations is demonstrated in the following cases. Cases 3 and 10 had arm-tongue circulation rates well above the maximum for normal. In spite of the prolongation of arm-tongue times the women denied symptoms of cardiac insufficiency. They subsequently developed marked cardiac failure. These observations indicate the interrelation between circulation time and cardiac insufficiency, and demonstrate the advantage of an objective method for the determination of circulatory insufficiency in contrast with the relatively inaccurate history obtained from some of the patients.

Arm-tongue circulation rate was used once to rule out cardiac decompensation in a patient who was very desirous of an abortion. This woman was a para iv gravida v who entered the hospital in her second month of gestation with a history of having had two therapeutic abortions at two different hospitals and being unable to do any housework at all because of severe dyspnea. The woman was very obese, weighed 244 pounds and was 60 inches tall. Physical examination did not reveal any findings of heart disease or cardiac failure. The arm-tongue circulation rate was 12.8 seconds and the arm-lung time 3.8 seconds (within normal limits). Replies to our inquiries from the two hospitals did not corroborate her statements. This further emphasized our diagnosis of malingerer. The patient was discharged without interrupting the gestation.

At no time did we encounter any prolongation of the arm-lung circulation rate. Evidently there was no failure of the right side of the heart in any of the cases in this series. Even among those women with increased arm-tongue times the arm-lung times were within normal figures.

Case 8 illustrated an extremely interesting manifestation of apparent left heart failure induced by an overactive right heart during the twenty-ninth week of gestation. The patient had been well compensated all along until she undertook a walk of approximately three miles at a fast pace. She suddenly became dyspneic and cyanotic, and began to cough up frothy fluid. She was immediately hospitalized and given $\frac{1}{4}$ gr. of morphine sulphate, $\frac{1}{75}$ gr. of atropine sulphate and 50 c.c. of 50 per cent glucose intravenously. Within two hours her condition had improved so considerably that she was well able to leave the hospital in good condition by the third day after admission.

McGinn and White[18] have described a series of six cases where pulmonary edema developed in the presence of uncomplicated mitral

stenosis. It was their contention that there is a considerable difference in prognosis between those cases where the left ventricle is still efficient and those cases of pulmonary edema where there is enlargement and failure of the left ventricle. The pulmonary edema which develops in cases with an intact left ventricle is induced by effort, excitement or paroxysmal tachycardia. The strong right ventricle of these hearts expels more blood into the pulmonary circuit than can be passed through the stenosed mitral valve. Such patients may show only cardiac asthma and in extreme instances pulmonary edema. Pulmonary edema appears at an earlier age and has a better prognosis in uncomplicated mitral stenosis than in those patients with enlargement and failure of the left ventricle.

It is also interesting to note that this patient was delivered at another hospital and went into pulmonary edema immediately after delivery. Again, she responded favorably to therapy within several hours. It would seem likely that the same mechanism which produced pulmonary edema during the twenty-ninth week of pregnancy was also responsible for her acute failure following labor. A fact which corroborates this conception is that between her attacks of pulmonary edema she was perfectly compensated, the arm-tongue and arm-lung times being within normal figures.

In attempting to show the value of circulation time studies to prognosticate the onset of cardiac failure, we found the method not always feasible. For example, Cases 15 and 8 had normal circulation times throughout pregnancy although both women went into cardiac failure, one during labor and the other immediately post partum. The cause of the cardiac failure in Case 8, immediately post partum, was the same as the cause of the attack of pulmonary edema she suffered during her twenty-ninth week of pregnancy. In Case 15, the normal circulation time figures were due to the fact that the patient was on prolonged bed rest of five months, during which time her weakened myocardium was adequate. However, the increased strain of labor producing cardiac failure indicated the true state of affairs.

It has long been known even in nonpregnant cardiacs that patients who are well compensated may develop a mild degree of decompensation with the onset of an upper respiratory infection. The occurrence of an upper respiratory infection during the thirty-eighth week of pregnancy in Case 6 was responsible for the abnormal prolongation of the arm-tongue time (17.4 seconds). The patient complained of increased dyspnea at that time. The following week the respiratory infection cleared, the arm-tongue time dropped to thirteen seconds and the patient was improved subjectively.

### CONCLUSIONS

1. The arm-tongue circulation rate in pregnant women with well-compensated rheumatic heart disease is within normal limits.

2. The arm-tongue circulation rate in pregnant women with cardiac insufficiency is prolonged.

3. The arm-lung circulation rate in pregnant women with well-compensated rheumatic heart disease is within normal limits.

4. The arm-lung time in cardiac insufficiency (Class 2b) remains within normal limits.

5. Increase of the arm-tongue circulation rate above normal despite a denial of symptoms of cardiac weakness is an indication of present circulatory insufficiency.

6. The use of arm-tongue circulation time tests was valuable as an objective method of eliminating a patient who was desirous of an induced abortion on the basis of assumed cardiac failure.

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15 CLARKE PLACE
1147 HOE AVENUE
1075 GRAND CONCOURSE

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**Tyler, G. T., Jr.:** **Endometrioma of the Umbilicus Following Caesarean Section,** South. M. J. **31**: 987, 1938.

The indication for cesarean section in a 26-year-old woman was an obstructed pelvic outlet caused by a displacement of one of the pubic rami following a fracture of the pelvis, sustained several years previously.

Three years after the operation the patient complained of a bloody discharge from the umbilicus which appeared at the time of her menses. There was a reddish swelling of the umbilicus. The clinical diagnosis of umbilical endometrioma was confirmed by biopsy. Thorough abdominal and pelvic examination revealed no other palpable evidence of ectopic endometrial tissue. The uterus was small and in retroposition.

Apparently the umbilical lesion developed as a direct transplant at the time of abdominal delivery. The suggestion is made that when midline incisions are employed in cesarean section, bayonet-like extension should be made to avoid the umbilicus. Other precautions against transplants of endometrial tissue consist in protecting the wound edges and abdominal cavity by gauze packs, and saline irrigation of the field following peritoneal closure in order to remove mechanically remnants of blood or uterine tissue.

ARNOLD GOLDBERGER

# CLASSIFICATION AND TREATMENT OF THE ANEMIAS OF PREGNANCY

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A NEMIA is a frequent complication occurring in the course of pregnancy. Realizing the importance of this, a study was conducted on the Obstetrical Service of Bellevue Hospital during the period extending from October, 1937, to July, 1938.

During this interval 881 pregnant women were studied according to the method to be described later. Four hundred twenty-five, or 48 per cent, of these women were found to have anemia on admission to the hospital during labor. The incidence of anemia rose to 72 per cent in the group receiving no active iron therapy during the ante-partum period.

## METHOD OF STUDY

A red blood count and hemoglobin determination were done, by a technician employed for this study, on every patient admitted to the prenatal clinic of Bellevue Hospital. The Sahli hemoglobinometer was used in determining the level of the hemoglobin, 14.5 gm. per 100 c.c. of blood being considered as 100 per cent. The red blood count and hemoglobin were rechecked by the same technician between the seventh and eighth months of gestation. If the red blood count was found to be below 4 million or the hemoglobin below 80 per cent, that patient was considered to have anemia. Five grains of ferrous sulfate* was prescribed three times daily for every patient developing anemia in the ante-partum period. This therapy was continued until the end of pregnancy or until symptoms of intolerance to the iron, such as nausea, vomiting, diarrhea, or heartburn developed.

On admission to the hospital during labor, a red blood count, hemoglobin determination and hematocrit were done by a fourth-year medical student. The red count, hemoglobin and hematocrit were repeated on the eighteenth day post partum by our technician. Some of the patients showing anemia on admission to the hospital in labor were given iron therapy during the post-partum period. Others, however, were used as a control group and no iron was prescribed.

Forty-two patients were detained in the hospital during their prenatal period for intervals varying from one week to three months, during which time red blood counts, hemoglobin determinations, hematocrit and plasma protein studies were done three times weekly, by the same technician. In this group the same determinations were repeated every other day during the first ten days post partum. In 48 patients gastric analyses were done ante partum and repeated on the eighth day post partum.

The hematocrit was done with the Wintrobe tube using the technique described by Wintrobe. Six milligrams of ammonium oxalate and 4 mg. of potassium oxalate per 5 c.c. of blood were used as anticoagulant. Using this solution, the volume of the erythrocyte remained unaltered.

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*Ferrous sulfate used in the treatment of these patients was given in the form of "hematinic plastules," plain.

## CLASSIFICATION OF THE ANEMIAS

The classification presented here is one derived from the study of the hematocrit on 99 patients. It depends entirely on the size of the red blood cell and the amount of hemoglobin contained in the cell. Details of this phase of the subject will be discussed later in a separate paper.

Classification of the Anemias of Pregnancy:

| | | | | | |
|---|---|---|---|---|---|
| I. Macrocytic | 62 per cent | | III. Microcytic | 2 per cent |
| a. Simple | 47 per cent | | a. Simple | 1 per cent |
| b. Hypochromic | 9 per cent | | b. Hypochromic | 1 per cent |
| c. Hyperchromic | 6 per cent | | | |
| II. Normocytic | 37 per cent | | | |
| a. Simple | 13 per cent | | | |
| b. Hypochromic | 23 per cent | | | |
| c. Hyperchromic | 1 per cent | | | |

It is interesting to note that macrocytosis occurred in 62 per cent of the anemias of pregnancy encountered during this study. Dieckmann and Wegner also found that in the period of gestation from ten to thirty-five weeks the erythrocytes differ from the average normal in that they are a little larger and contain more hemoglobin.

In 47 per cent of the group showing macrocytosis the mean corpuscular hemoglobin remained normal or very slightly reduced. The mean corpuscular hemoglobin concentration, however, was below normal because the increase in size of the red blood cell was not associated with a corresponding increase in hemoglobin. In 9 per cent there was a moderate to marked decrease in both mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, resulting in hypochromia. In 6 per cent the size of the red cell and the amount of hemoglobin were both increased. It appears from this study that the milder forms of the macrocytic hyperchromic anemias of pregnancy may be diagnosed more readily if hematocrit determinations are done.

In 37 per cent the size of the red blood cell remained within normal limits. Here again the hemoglobin content of the cell was normal, reduced or increased in amount.

Microcytosis was found to occur in only 2 per cent. One of these was associated with marked hypochromia.

## TREATMENT

Analysis of the effect of iron on the anemias of pregnancy: 881 pregnant women are included in this study; 325 received iron in the form of ferrous sulfate, 5 gr. three times daily, one-half hour after meals, during the prenatal period. The average duration of iron therapy was 53.31 days. Five hundred and fifty-six received no iron. Patients receiving iron less than ten days were included in this non-treated group.

Four hundred and twenty-five, or 48 per cent, of all patients admitted to the hospital during labor had an anemia. Of the 325 patients receiving iron ante partum, 28 per cent were found to have a mild anemia on admission to the obstetric service during labor. However, of the total number of 307 pregnant women receiving *no iron* therapy prenatally, 72 per cent were found to have an anemia. Four hundred and fifty-six patients had normal readings of the red blood count and hemoglobin at the time of admission during labor and 55 per cent of this group had received no iron during the prenatal period.

Table I shows the results of treatment with iron during the prenatal period in 325 pregnant women who had anemia. Group A represents 118 parturient women who received iron prenatally, but who continued to show a mild anemia on admission during labor. The average red blood count during the prenatal period, before the start of iron therapy, in this group was 3.65 M and the average hemoglobin was 65.82 per cent (9.54 gm.). On admission during labor the average red blood count rose to 3.88 M and the average hemoglobin to 77 per cent (11.17 gm.), an increase of 0.25 million in red blood cells per c. mm. and 1.63 gm. in hemoglobin per 100 c.c. of blood.

Group B consists of 207 women who had an anemia during the prenatal period and who received iron. At the start of iron therapy the average red blood count was 3.73 M and the average hemoglobin 66 per cent (9.56 gm.). On admission to the hospital during labor, the red blood count and hemoglobin were at normal levels, the average red blood count being 4.31 million per c. mm. and the average hemoglobin 83.1 per cent (12.05 gm.). This represents an increase of 0.58 million red blood cells per c. mm. and 2.49 gm. of hemoglobin per 100 c.c. of blood.

TABLE I.—RESULT OF THERAPY WITH IRON DURING THE PRENATAL PERIOD OF 325 PATIENTS HAVING SECONDARY ANEMIA OF PREGNANCY

| GROUP | NUMBER | DAYS OF IRON THERAPY | AT START OF THERAPY DURING PRENATAL PERIOD | | | DURING LABOR | | |
| | | | R.B.C.–MILLIONS PER C. MM. | HB | | R.B.C.–MILLIONS PER C. MM. | HB | |
| | | | | % | GM. | | % | GM. |
| A | 118 | 46.62 | 3.63 | 65.82 | 9.54 | 3.88 | 77.0 | 11.17 |
| B | 207 | 60.00 | 3.73 | 66.08 | 9.58 | 4.31 | 83.1 | 12.05 |
| Average | 325 | 53.31 | 3.68 | 65.95 | 9.56 | 4.09 | 80.05 | 11.61 |

TABLE II.—RED BLOOD COUNT AND HEMOGLOBIN CURVE ON 307 PREGNANT WOMEN RECEIVING NO IRON DURING THE PRENATAL PERIOD

| NUMBER | PRENATAL PERIOD | | | DURING LABOR | | |
| | R.B.C.–MILLIONS PER C. MM. | HB | | R.B.C.–MILLIONS PER C. MM. | HB | |
| | | % | GM. | | % | GM. |
| 152 | 3.06 | 47.6 | 6.90 | | | |
| 307 | | | | 3.01 | 56.25 | 8.16 |

For the entire group of 325 parturient women who received iron ante partum, the average red blood count was found to rise from 3.68 M at the onset of iron therapy to 4.09 M on admission during labor. Similarly the average hemoglobin rose from 65.95 per cent (9.56 gm.) to 80.05 per cent (11.61 gm.). This suggests that 1 gm. of ferrous sulfate given daily during the prenatal period to patients developing anemia will produce a definite rise of the red blood count and hemoglobin.

In contrast, Table II represents the average blood picture seen in 307 pregnant women who received no iron during the prenatal period; 152 of these women who were seen ante partum were found to have an average red blood count of 3.06 M and an average hemoglobin of 47.6 per cent (6.90 gm.). In comparing these red blood count and hemoglobin readings taken during comparable prenatal periods, it is seen that the severity of the anemia in the nontreated group is greater than either of the Group A or B who received iron prenatally (Figs. 1 to 3). This suggests that iron therapy will not only cause an increase in the red blood count and hemoglobin but even if completely normal levels are not reached, a further decrease in the levels of the red blood count and hemoglobin is prevented.

The level of the red blood count and hemoglobin during labor in this nontreated group is seen to be strikingly lower than in the group receiving iron (Figs. 2 to 4). The average red blood count per c. mm. was found to be 3.01 M. and the average hemoglobin was 56.25 per cent (8.16 gm.).

Among the 325 women who received iron ante partum, only 61 patients had a normal red blood count before the start of iron therapy, but on admission to the hospital in labor, 234 were found to have a normal red blood count (Figs. 1 and 2). Similarly 224 had normal levels of hemoglobin during labor contrasted to 4 during the prenatal period before the onset of iron treatment (Figs. 3 and 4).

Only 27 of the 307 patients who received no iron in the ante-partum period had a normal red blood count (Fig. 2), and only 67 were found to have normal hemoglobin determinations during labor (Fig. 4). In contrast, among the group of 325
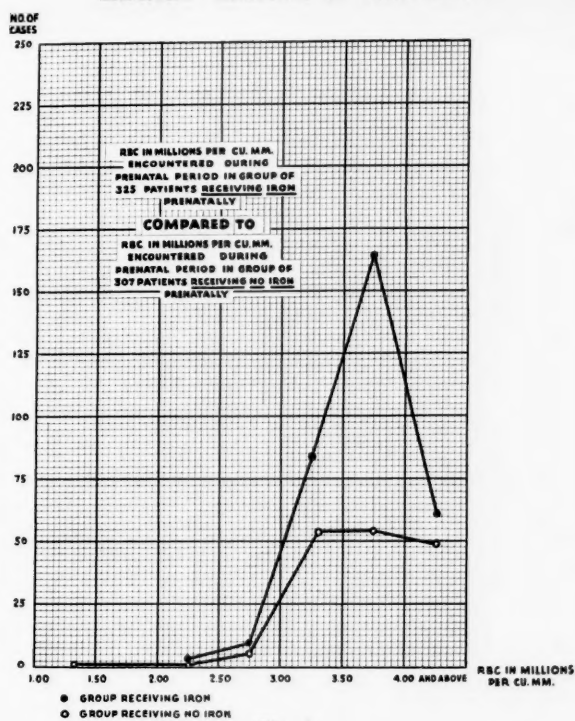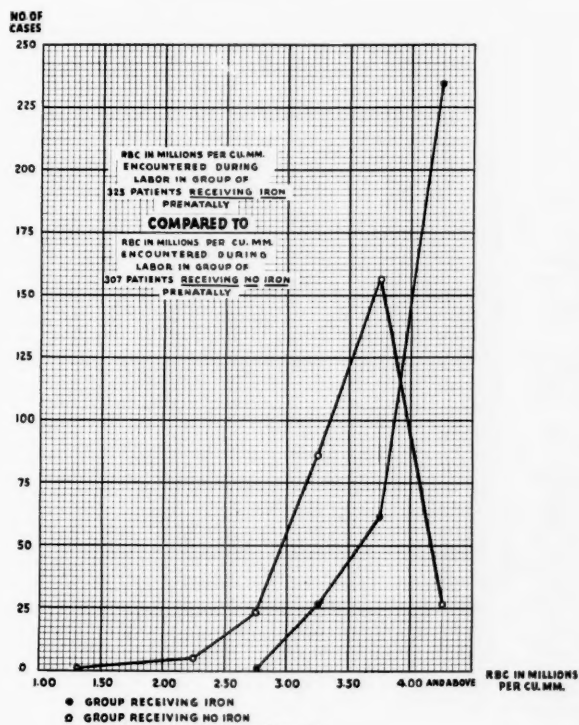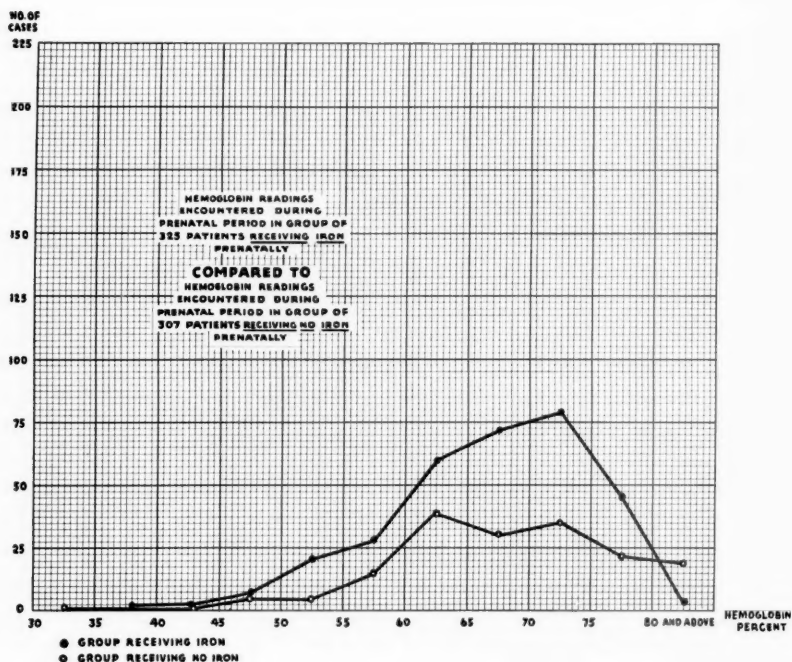
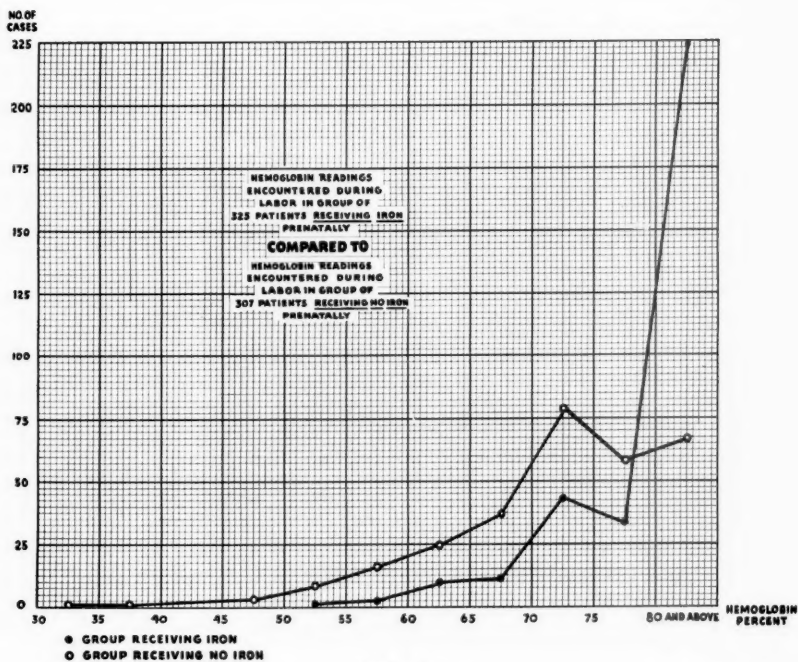Fig. 1.



Fig. 2.

Fig. 3.



Fig. 4.

women receiving iron prenatally, 234 had normal red blood cell levels and 224 had normal hemoglobin readings on admission to the hospital while in labor (Figs. 2 and 4). Only 1 patient among this treated group had a red blood count below 3.00 million during labor, whereas 29 had counts below this figure in the group receiving no iron ante partum (Fig. 2). There were 3 patients among the treated group who had hemoglobin readings below 60 per cent compared to 29 in the nontreated group (Fig. 4). Further scrutiny of Figs. 1 to 4 shows clearly the lower levels in red blood count and hemoglobin in the group of patients who did not receive the benefit of iron prenatally. The hemoglobin levels reached as low as 30 per cent and the red blood count as low as 1.35 per cent in the nontreated group.

### ROLE OF DIET IN THE TREATMENT OF THE ANEMIAS OF PREGNANCY

It is extremely difficult to control the diets in the group of patients who attend the prenatal clinic in Bellevue Hospital. Therefore each patient was questioned closely about her diet, an attempt being made to determine the proportion of meat, fresh vegetables, fruits, milk, and eggs in the daily dietary. Based on this questionnaire the diets were labeled as adequate, fair, or inadequate. Patients eating red meat, eggs, fresh fruits and vegetables, and one quart of milk daily were considered to have an adequate diet. Patients eating meat and eggs several times weekly, fresh fruits and vegetables daily, and 1 quart of milk daily were considered as having a fair diet. Patients eating foods low in protein and in iron content were considered as having inadequate diets.

The cases were further subdivided into noncomplicated and those complicated by diabetes, syphilis, pre-eclampsia, pyelitis, cardiac disease, etc.

A table was constructed to show the value of an adequate diet in aiding in the control of the anemias of pregnancy. The noncomplicated cases receiving iron during the prenatal period were found to be little affected by diet. Iron therapy produced an increase in the levels of the red blood cells and hemoglobin regardless of whether or not the patient was partaking of an adequate, fair, or inadequate diet. Iron which was given during the prenatal period apparently was sufficient to compensate for the lack of sufficient amounts of iron in the dietary. However, cases which were complicated by one of the frequent prenatal complications such as pre-eclampsia, pyelitis, etc., required the addition of an adequate diet rich in iron and protein. This group of patients having some form of prenatal complication and receiving only a fair or inadequate diet tended to show a persistence of the anemia in spite of iron therapy.

The effect of an adequate diet was more noticeable in the group of patients who received no iron prenatally. The average red blood count and hemoglobin were found to decrease slightly as the diet became less satisfactory. Thus in the group receiving an adequate diet the average red blood count per c. mm. was 3.69 million and the average hemoglobin 71.18 per cent; in the group receiving a fair diet the average red blood count was 3.57 million and the average hemoglobin 70 per cent; in the group partaking of an inadequate diet the average red blood count was 3.52 million and the average hemoglobin 68 per cent. The drop in the average red blood count and hemoglobin was more apparent in the group of patients who had some prenatal complication such as pre-eclampsia, pyelitis, or syphilis. In this group, the patients receiving an inadequate diet had an average red blood count of 3.08 million and an average hemoglobin of 59 per cent. The patients receiving an adequate diet, however, had an average red blood count of 3.67 million and an average hemoglobin of 69 per cent.

VALUE OF IRON IN THE POST-PARTUM PERIOD

The group of patients who received iron during the prenatal period appeared to withstand the effects of labor better than the group who did not receive iron and who subsequently entered in labor with an anemia. This statement is made on the basis of comparison of the morbidity and length of hospitalization, post partum. Morbidity was determined on the 100°, 100.4° and 101° F. standards. There were 14.8 per cent of the patients who were prepared prenatally with iron therapy who ran a morbid course post partum. The nontreated group that entered in labor with an anemia had a 19.5 per cent morbidity. Similarly the length of hospitalization post partum was greater in the nontreated group. The average number of hospital days was 10.35 in the group of patients receiving iron during the ante-partum period, and 11.05 in the group receiving no iron.

The patients in Bellevue Hospital are kept ten days post partum, and then discharged. The period is too short to determine any significant immediate effects of iron given during this short post-partum period. Immediately following delivery, some patients having an anemia, i.e., a red blood count of less than 4 million per c. mm. or a hemoglobin less than 80 per cent, were given 5 gr. of ferrous sulfate three times daily, while others, used as a control group, were not given iron. The red blood count and hemoglobin determination were repeated on the eighth day post partum. Little significant difference could be noted during this short period between the group receiving iron and the group receiving no iron post partum.

There was a slight rise in the red blood cells per cubic millimeter and in the hemoglobin on the eighth post-partum day in both the treated and nontreated groups. However, the group receiving iron post partum had an average red blood count per c. mm., 0.01 million higher and an average hemoglobin 4 per cent (0.58 gm.) higher than the group receiving no iron.

One gram of ferrous sulfate daily was given to approximately half of the post-partum patients with anemia for a four-weeks period following discharge from the hospital. At the end of this time the patients receiving iron showed slightly higher levels of the red blood cells and hemoglobin than those patients who were not given the benefit of iron therapy.

DISCUSSION

Iron is of decided value in the treatment of anemia developing during pregnancy. Ferrous sulfate, 5 gr. three times daily, given one-half hour after meals, is the minimum dose to be used.

A small percentage of patients, however, will not respond with a complete return to normal of the red blood count or hemoglobin during the prenatal period. A mild form of anemia may continue until after delivery, but by the eighth day post partum there is a tendency for spontaneous resumption of normal levels in the red blood cells, hemoglobin and the hematocrit. Whether this lowered level of the red blood count and hemoglobin in the latter part of pregnancy is entirely physiologic and due to hydremia is difficult to determine. Studies in plasma proteins which were done would lead one to believe that the rise in the red blood count and hemoglobin after delivery is due partially to concentration of the blood resulting from the loss of fluids.

Bethell found that with the hematocrit value as a basis for calculation and on the assumption that there occurs no compensatory output of red blood cells, the lowest red blood count that may be explained solely by hydremia is approximately 3.7 M, the lowest hemoglobin is about 70 per cent. Dieckmann and Wegner and others believe that a 10 to 20 per cent lowering of hemoglobin during pregnancy may be the result of hydremia and may not represent true anemia.

These patients who appeared to be resistant to the effects of iron were given 30 gr. of ferrous sulfate daily and a high caloric diet with liver daily. After seven- to ten-days trial with this form of therapy, 3 c.c. of concentrated liver extract (10 units) was given intramuscularly daily for five days and then 3 times weekly for twenty-one days. Vitamin $B_1$ was given intramuscularly daily. If the gastric analysis showed low levels or absence of free hydrochloric acid, dilute hydrochloric acid was given by mouth. In spite of this intensive treatment a mild form of anemia persisted. Bethell also noted many instances in which the administration of iron failed either to correct or prevent anemia. These cases were found frequently to possess red blood cells of relatively large volume. However, these subjects when placed on a suitable diet (65 gm. of protein with 1 quart milk added) developed correction of the anemia with restoration of the erythrocyte volume.

Maurice Strauss believes that the hypochromic anemias of pregnancy may be completely relieved by the administration of iron in suitable doses. Corrigan and Strauss state that the hypochromic anemias in pregnancy may be prevented largely by routine iron especially in the latter months and so advise the prophylactic use of iron. Evans also testifies for the value of iron in the treatment of the anemias of pregnancy. He believes that the great majority of the anemias of pregnancy are preventable by adequate doses of inorganic iron and he too advises that "all women during pregnancy should be given inorganic iron, particularly during the last trimester." Bethell reports that anemia in pregnancy due to iron depletion may be cured by supplying iron in adequate doses.

We do not subscribe to the practice of giving iron to all women during pregnancy with the hope of preventing the development of anemia. Since one-half of the women during pregnancy do not develop anemia it does not seem reasonable to give all pregnant women iron. It is sounder practice to check on the status of the red blood count and hemoglobin several times during the course of pregnancy, as we have done, and prescribe iron only when required.

The value of dilute hydrochloric acid in the treatment of the anemias of pregnancy is questionable.

Evans suggests the use of dilute hydrochloric acid, 10 drops three times daily increasing to 40 drops, particularly during the last trimester. Mettier and Minot claim that the iron does not need to be given in an acid medium, for apparently if a sufficient dose of iron is given in an alkaline medium suitable responses of the bone marrow will ensue. However, their studies do indicate that soluble iron compounds are absorbed from the gastrointestinal tract, or utilized more readily for blood formation when administered with acid rather than with alkaline meals.

### SUMMARY AND CONCLUSIONS

1. This is a study of 881 pregnant women, 325 of whom received 5 gr. of ferrous sulfate three times daily during the prenatal period.

2. Four hundred twenty-five, or 48 per cent, of all patients in labor were found to have an anemia on admission to the hospital. Seventy-two per cent of this number of patients showing anemia had received no iron during the prenatal period.

3. Three hundred twenty-five patients who received iron therapy during the prenatal period were found to have an average red blood count of 4.09 M and an average hemoglobin of 80.05 per cent (11.61 gm.) on admission during labor.

4. Three hundred seven patients who received no iron during the prenatal period were found to have an average red blood count of 3.01 M and an average hemoglobin of 56.25 per cent (816 gm.) on admission during labor.

5. The group of patients receiving *no* iron during the prenatal period showed far lower levels in the red blood cells and in hemoglobin than the group receiving iron. In the former group the lowest red blood count was 1.35 M and the lowest hemoglobin 30 per cent.

6. Macrocytosis was found to be present in 62 per cent of the cases showing anemia. Only 7 per cent of these anemias showed hyperchromia.

7. Inorganic iron in the form of ferrous sulfate, 1 gm. daily, is effective in restoring the red blood count and hemoglobin to normal levels.

8. An adequate diet in itself will not prevent the development of anemia during pregnancy.

9. One gram of ferrous sulfate which is given during the prenatal period apparently is sufficient to compensate for the deficient amount of iron in an inadequate diet.

10. The group of anemic patients receiving iron during the prenatal period had a 14.8 per cent morbidity as compared with 19.5 per cent morbidity in the nontreated group.

11. The average number of days of hospitalization was 10.35 in the patients receiving iron prenatally and 11.05 in the patients receiving no iron ante partum.

12. Iron therapy must be continued beyond the period of hospital stay to have any significant effect on the red blood cells and hemoglobin of the post-partum anemic patient.

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# THE EXCRETION OF FREE AND ACETYLSULFANILAMIDE IN HUMAN BREAST MILK[*][†]

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IN AN earlier paper[1] a study was made of the excretion of sulfanilamide in the breast milk of twenty patients who had received orally a total of 2 or 4 gm. (30 or 60 gr.) of the drug in two equal, four-hourly doses. Of the 10 patients who received the 2 gm. dose, the total amount of drug excreted in the milk varied from 3.76 to 13.67 mg.; of those who received the 4 gm. dose, the variation was from 11.77 to 54.00 mg. In terms of milligrams per cubic centimeter, the variation was from 0.006 to 0.016 and from 0.019 to 0.040 mg. per c.c. With the doubled dose of drug, considerably more than a double amount of the drug was excreted in the milk.

The purpose of the present investigation was to determine whether prolonged use of sulfanilamide at therapeutic blood levels would result in an accumulation of the drug in breast milk sufficient to be detrimental to the nursing baby.

In the previous paper, the free sulfanilamide levels in the blood and milk were compared, and it was shown that although they followed the same general course, the levels in the milk were considerably higher than those in the blood. The drug continued to be excreted in the milk even after the blood levels were negligible, but the largest total amount of drug excreted in the milk was only 1.5 per cent of that ingested (Charts 1 and 2).[1]

It was stated that sulfanilamide was excreted in the milk as in the urine partly in the unchanged and partly in the conjugated form, but quantitative determinations for the acetyl compound were not given. Since it is known that, at least in animals, the toxicity of acetylsulfanilamide is greater than that of the free sulfanilamide,[2] it was felt that further information concerning the amount of drug excreted in the conjugated form might be of value. The present study, therefore, includes graphs which compare both the free and acetylsulfanilamide levels of the blood, milk, and urine.

The patients considered were normal women studied during the third to ninth post-partum days. Since it was customary for the patients to leave the hospital on the tenth day, it was impossible to continue the study for a longer period. Two to 5 gm. of the drug were administered in 6 doses daily for a period of three days. By

this procedure it was hoped that a fairly constant blood level might be established for comparison with the milk level. The milk was collected at four-hour intervals (alternate breasts were emptied by an electric breast pump) and determinations for both free and conju-
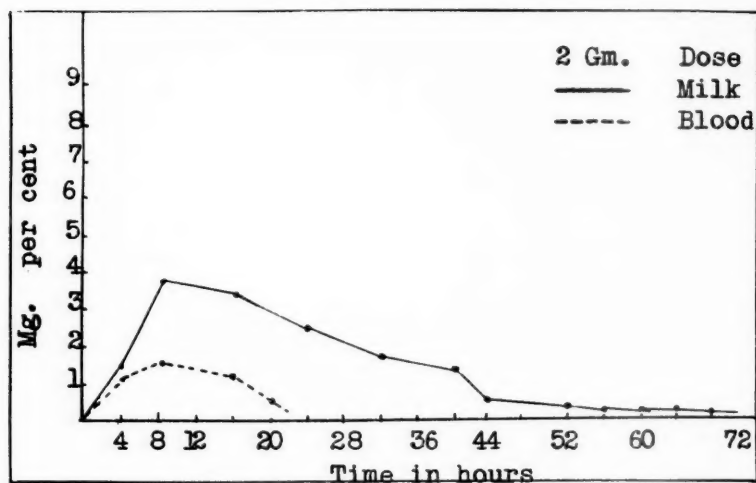


Chart 1.—Comparison of free sulfanilamide levels in the blood and milk. Dose 2 gm. (30 gr.).



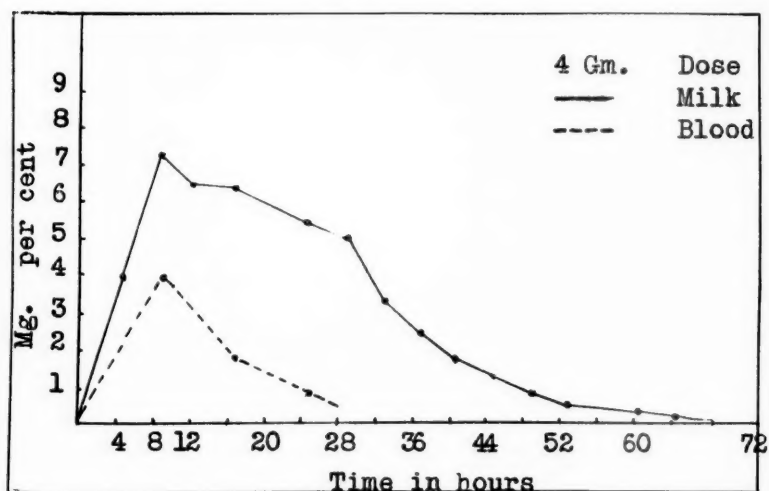Chart 2.—Comparison of free sulfanilamide levels in the blood and milk. Dose 4 gm. (60 gr.).

gated sulfanilamide were made on each specimen. Blood was obtained twice the first day, eight and sixteen hours after medication had been begun, and at twenty-four-hour intervals thereafter. More blood determinations would have been of value, but patients objected to more frequent venipuncture. Collections of milk, blood and urine

were continued, for two or more days after the drug had been discontinued, i.e., a total of at least five days. The levels of both free and acetylsulfanilamide in the blood and milk were compared and the total amounts of the drug excreted in the milk and urine were determined.

The method for determination of free and conjugated sulfanilamide in the blood and urine was that described by Marshall[3] with the improvement recently suggested by him[4]; namely, the use of buffered ammonium sulfamate for the destruction of the excess nitrous acid. This modification has greatly improved the original method and makes for a much better color match. The method for the determination of free sulfanilamide excreted in the milk was the same as that described by us[1] earlier except that the dilution was 1:10 instead of 1:5, and the buffered ammonium sulfamate was incorporated. The procedure was briefly as follows:

To 5 c.c. of milk in a centrifuge tube was added 2.5 c.c. of a 20 per cent solution of p-toluenesulfonic acid. The solutions were mixed, allowed to stand overnight at room temperature, and then centrifuged and filtered. One and one-half cubic centimeters of the clear supernatant liquid was pipetted into a flask and diluted with 9 c.c. of distilled water and 0.5 c.c. of p-toluenesulfonic acid. To this solution was added 1 c.c. of a 0.1 per cent solution of sodium nitrite and after three minutes, 1 c.c. of a 1 M solution of sodium dihydrogen phosphate containing 0.5 per cent of ammonium sulfamate ($NaH_2PO_4 \cdot H_2O$, 13.8 gm., ammonium sulfamate 0.5 gm.). After two minutes 5 c.c. of a solution of dimethyl $\alpha$ naphthylamine (1 c.c. in 250 c.c. of 95 per cent ethyl alcohol) was added. After fifteen to thirty minutes the colors were compared with a suitable standard. Ordinary breast milk to which definite concentrations of sulfanilamide had been added and then treated in the manner just described was used as a standard.

In order to determine the acetylsulfanilamide, a 1:20 dilution was used. To 1.5 c.c. of the clear supernatant liquid was added 15 c.c. of water and 3.5 c.c. of p-toluenesulfonic acid and the solution heated in a boiling water bath for ninety minutes. The standard was heated in the same manner. The solutions had a faint brownish tinge, but since the standard was treated in the same way, it was not difficult to get a good color match. After the solutions had cooled, the procedure was the same as that for the determination of free sulfanilamide except that a 2 M buffer containing 0.5 per cent ammonium sulfamate was used instead of the 1 M buffer.

The 25 patients studied have been divided into three groups, depending upon the amount of drug received (Table I).

TABLE I. DIVISION OF PATIENTS ACCORDING TO SULFANILAMIDE DOSAGE

| GROUP | NO. PATIENTS | SINGLE DOSE GM. | DAILY DOSE GM. | TOTAL DOSE GM. |
|-------|-------------|--------------|-------------|-------------|
| I | 10 | 0.35* ( 5 gr.) | 2 (30 gr.) | 7.33 (110 gr.) |
| II | 5 | 0.66 (10 gr.) | 4 (60 gr.) | 12.00 (180 gr.) |
| III | 10 | 0.80 (12.5 gr.) | 5 (75 gr.) | 15.00 (225 gr.) |

*In order to reach the desired blood level rapidly, these patients received 0.66 gm. (10 gr.) each for the first four doses.

Chart 3 compares the excretion of the right and left breasts separately. Milk was obtained every four hours, but since the breasts were pumped alternately, the determination for each specimen was a level for the preceding eight hours. As can be seen the general direction of the curve for each breast was very similar, but there was a slight lag of one breast behind the other.

Charts 4, 5, and 6 compare the free and total sulfanilamide (free plus acetyl) in the blood and milk of a typical patient from each of
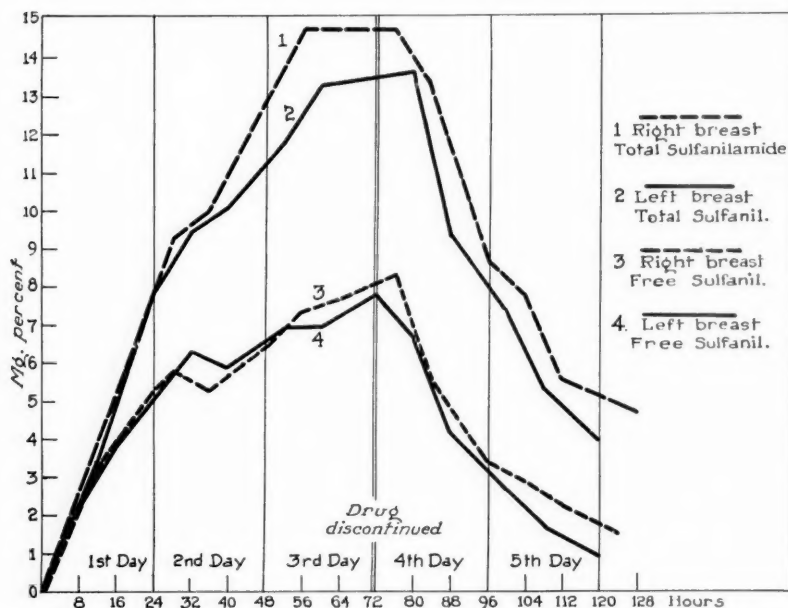


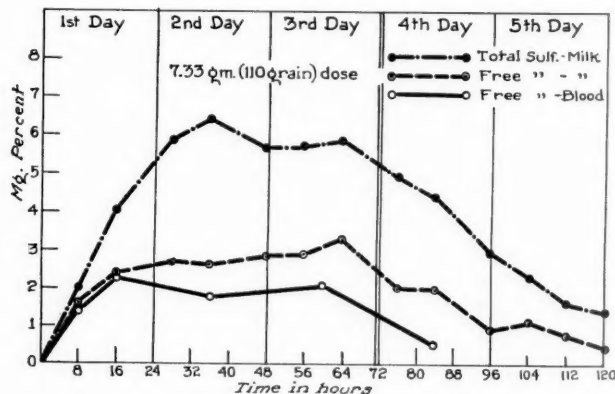Chart 3.—Comparison of the excretion of the sulfanilamide by the right and left breasts.



Chart 4.—Comparison of the free and total sulfanilamide (free plus acetyl) levels in the milk and blood. Dose 7.33 gm. (110 gr.).

the three groups studied. The comparison was made over a period of five days; three days during which the drug was administered and two days following. The blood level had usually been established within twenty-four hours and so a comparison of the second and third days should be fairly accurate.
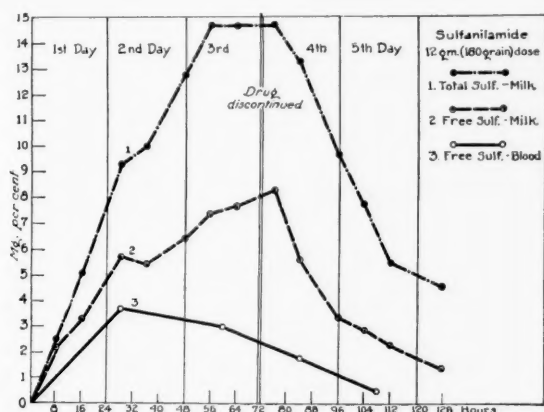


Chart 5.—Comparison of the free and total sulfanilamide levels in the milk and blood. Dose 12.0 gm. (180 gr.).
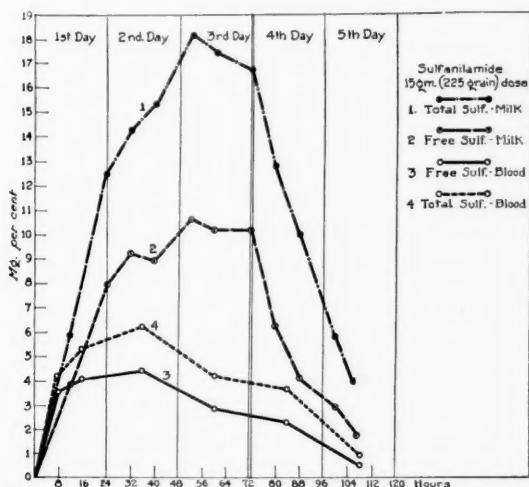


Chart 6.—Comparison of the free and total sulfanilamide levels in the milk and blood. Dose 15.0 gm. (225 gr.).

As in the series previously reported, it was noted that the free sulfanilamide level in the milk was considerably higher than that in the blood. In fact, in most cases it was at least twice as great, and with large doses seemed to be considerably more than twice. The total (free plus acetyl) level was still much higher. Table II shows this quite clearly.

TABLE II.   A COMPARISON OF THE VARIATION IN THE PEAKS OF THE SULFANILAMIDE
LEVELS IN THE BLOOD AND MILK (MG. PER 100 C.C.)

| GROUP | NO. PATIENTS | DAILY DOSE | FREE IN BLOOD | FREE IN MILK | TOTAL IN MILK* |
|-------|--------------|------------|---------------|--------------|----------------|
| I     | 10           | 2 gm.      | 2.15-2.50     | 2.97- 5.27   | 5.29- 9.25     |
| II    | 5            | 4 gm.      | 1.78-3.70     | 6.25-14.70   | 10.50-22.41    |
| III   | 10           | 5 gm.      | 3.24-7.68     | 6.28-16.66   | 9.25-28.57     |

*Free plus hydrolyzed acetyl.

Just why there was such a difference in the levels in the milk and blood cannot be explained, although the differences may not be as great as the graphs might lead one to believe. The milk and blood specimens were collected at the same time, but it cannot be assumed that the time relationship of the levels is absolute. The blood level is momentary, while the milk level may possibly represent a cumulation level for the previous eight hours.

A short time ago, Stewart and Pratt[5] reported their study of the excretion of free sulfanilamide in 28 normal convalescent women during the first eight post-partum days. Ten of their patients received 2 gm. (30 gr.) of sulfanilamide daily, and 18 received 4 gm. (60 gr.). From single daily blood and milk determinations, they concluded that in those who received 2 gm., "the concentration of free sulfanilamide in the breast milk corresponded closely to the estimations in the blood stream (2 to 4 mg. per 100 c.c.)." In those who received 4 gm., "the concentration of the blood showed greater variation (4 to 7 mg. per 100 c.c.) and the concentration in the milk was generally equal to or slightly higher than the blood." Their blood concentrations agree quite well with both our earlier and present observations with similar dosages, but we have consistently found the milk level to be considerably higher than that of the blood. This discrepancy may be due to the difference in the method of determination of the drug in milk.

Recently, Pinto[6] has reported determinations on 3 patients over a period of twenty-four hours. The levels in the milk were in agreement with ours. He gave no data on blood determination, but made the statement that "the concentrations of sulfanilamide in human milk after the ingestion of a single large dose of the drug, follows a course similar to that found by other workers for its concentration in the blood. The only difference is that the peak concentration in milk seems to lag behind that in the blood by several hours."

Since an appreciable amount of the drug was excreted in the milk in the acetyl form, it was of interest to determine whether there was any: Relationship between the percentage conjugated and (1) the amount of drug ingested; (2) the amount of drug excreted; (3) the volume of milk secreted; (4) the period in the course of the treatment.

From Chart 7, it can be seen that in the milk, blood and urine, the peaks for the excretion of the total sulfanilamide (free plus hydrolyzed acetyl) paralleled the free sulfanilamide peaks. Considering the individual variation in the absorption and excretion of this drug and its dependence upon fluid intake, correlation of the data on a

small number of patients is difficult. The relationship between the percentage of drug conjugated and the amount of drug ingested and excreted can best be observed from Table III, which gives the variations noted in each group of patients.
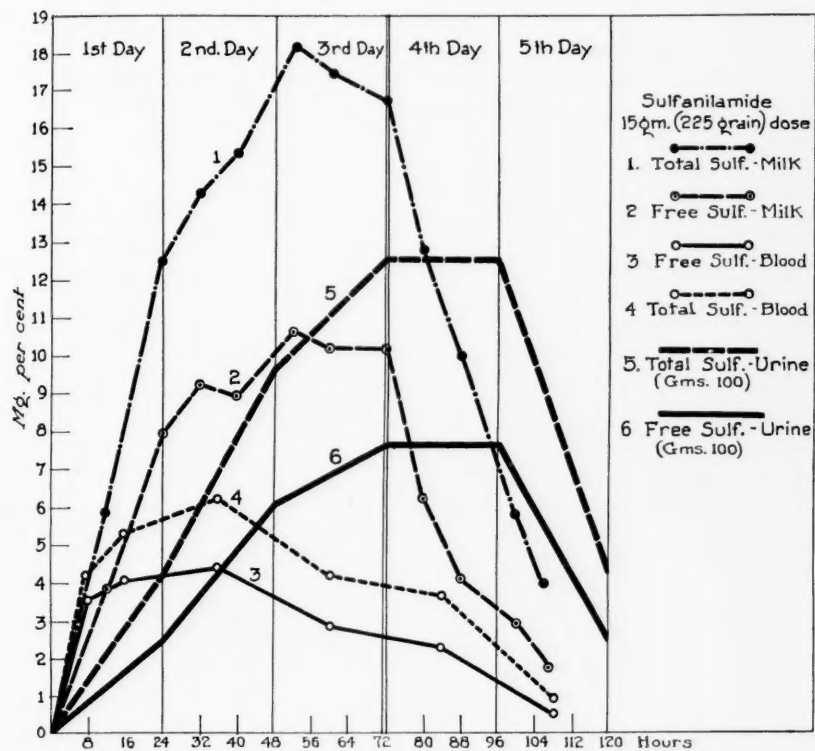


Chart 7.—Comparison of the free sulfanilamide peaks with the total sulfanilamide peaks in blood, milk and urine.
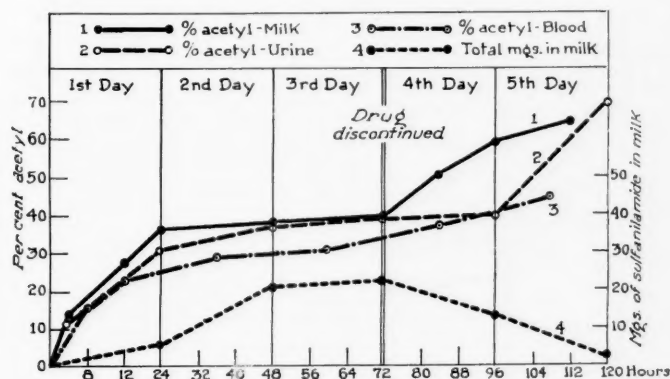


Chart 8.—Comparison of the percentage of the drug conjugated in the blood, milk, and urine during the course of the treatment.

Toward the end of the course of observations of the patients, i.e., during the fourth and fifth days when therapy had been discontinued and the amount of drug excreted was gradually decreasing, there was a sharp rise in the percentage of the drug conjugated (Chart 8).

The higher percentage conjugated toward the end of the course cannot be dependent upon the smaller total amount being excreted then, because there was only a relatively small amount being excreted at the beginning of the experiment when the percentage of acetyl was low. It would appear that if there was any storage of the drug in the body it was stored as the acetyl, or, at least, that the last traces of the drug were excreted as the acetyl derivative. In this respect it would be of interest to observe the percentage of acetyl excreted in the urine of patients with impaired renal function.
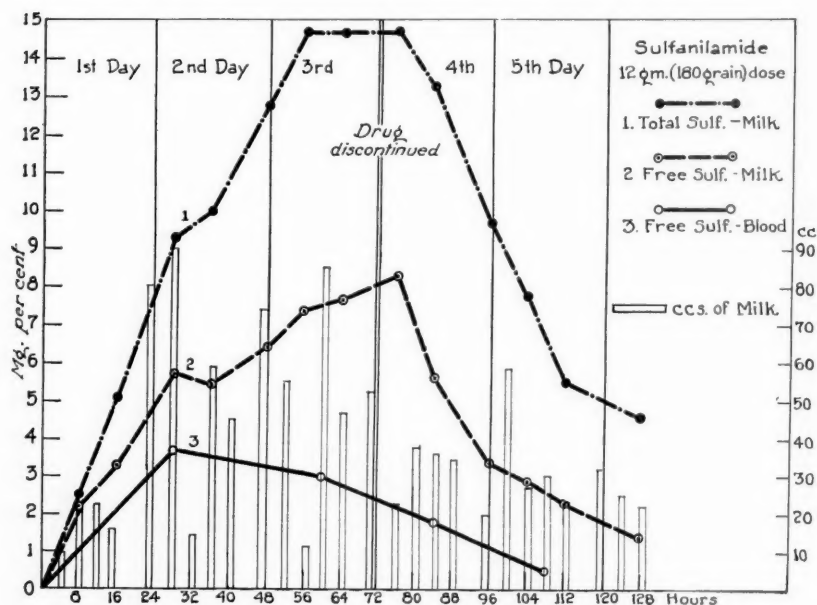


Chart 9.—Comparison of the concentration of the drug excreted with the volume of milk secreted.

Chart 9, of a patient typical of Group III, shows the relationship between the concentration of sulfanilamide in the milk and the volume of milk secreted. The variation in the amount of milk obtained at the 56-, 60-, 64-, 72- and 76-hour collections was from 12 to 87 c.c., yet the sulfanilamide level (free plus conjugated) remained constant at 14.7 mg. per 100 c.c. That is, if after the peak sulfanilamide level in the milk had been reached, the level in the blood were maintained fairly constant, the concentration per cubic centimeter of the drug in the milk remained the same whether the total volume of the milk were large or small. Further studies of this type might lead to a better knowledge of the mechanism of lactation.

TABLE III. THE RELATIONSHIP BETWEEN THE AMOUNT OF DRUG CONJUGATED AND THE AMOUNT OF DRUG INGESTED, THE AMOUNT OF DRUG EXCRETED AND THE VOLUME OF MILK SECRETED

| GROUPS | PATIENTS | TOTAL DOSE | EXCRETED IN MILK | MG. PER C.C. | TOTAL DOSE PER CENT | EXCRETED AS ACETYL |
|---|---|---|---|---|---|---|
| A | 10 | 2.00 gm. | 3.7- 13.7 mg.* | 0.006-0.02 | | |
| B | 10 | 4.00 gm. | 11.8- 54.0 mg.* | 0.02 -0.04 | | |
| I | 10 | 7.33 gm. | 38.7- 93.4 mg. | 0.04 -0.07 | 0.53-1.23 | 35.11-60.99% |
| II | 5 | 12.00 gm. | 50.3-166.4 mg. | 0.07 -0.18 | 0.45-1.40 | 35.34-46.00% |
| III | 10 | 15.00 gm. | 64.5-233.3 mg. | 0.11 -0.20 | 0.45-1.62 | 45.16-83.98% |

*Free sulfanilamide only.

No severe toxic symptoms were observed in any of our patients, but many of them became cyanotic. Many pediatricians feel that children tolerate the drug as well, if not better, than adults. Not much is known yet concerning the tolerance or later effects of the drug in the newborn. Helmholz[8] prescribed a dose of 0.33 to 0.50 gm. per day for infants. In the treatment of infants ill with meningococcus infection, Waghelstein[9] used a daily dose calculated on the basis of 250 mg. per kilogram of body weight. Long and Bliss[10] estimated that in severe infections, 1 gm. of sulfanilamide per 10 pounds of body weight should be received during the first twenty-four hours.

The largest amount of drug excreted in the milk in any case (Table III) was only 0.23 gm., 1.62 per cent of the total dose ingested, and that was in a patient whose blood level was 5 mg. per 100 c.c. It is quite difficult to maintain a blood level higher than this in patients without impaired renal function or without limitation of fluids.[11] Most patients in whom it is desirable to maintain a blood level higher than 5 mg. per 100 c.c. would probably be so ill that the baby would be removed from the breast anyway. None of the babies in our experiments were breast fed, but in the work of Stewart and Pratt[5] they were permitted to nurse. They observed no toxic manifestations in the babies.

In our previous paper we suggested that until more was known of the tolerance of the newborn for the drug, and until further work had been done upon the excretion of sulfanilamide during therapeutic dosage, breast feeding be discontinued during the period that the drug was being excreted in the milk. The present study has shown that an increased dose of sulfanilamide administered over a prolonged period does not greatly increase the percentage of the drug excreted, and since the total amount of drug excreted over a period of five days was never greater than 0.23 gm., it would seem that there is probably little danger to a nursing infant unless it is unusually susceptible to sulfanilamide.

## CONCLUSIONS

1. Sulfanilamide has been administered to 25 lactating women in therapeutic doses over a period of three days, and the free and acetyl-sulfanilamide levels determined in the blood, milk, and urine.

2. A method has been devised for the determination of free and acetylsulfanilamide in milk.

3. The level in the milk was considerably higher than that in the blood.

4. The drug was still being excreted in the milk in measurable, but negligible, amounts forty-eight hours after administration had been discontinued.

5. The percentage of the sulfanilamide excreted in the conjugated acetyl form was relatively low the first day the drug was administered, increased slightly the second and third days, and rose sharply the fourth and fifth days when administration of the drug had been discontinued. The percentage varied from 35.1 to 83.9. The same general course was observed in blood and urine.

6. After a fairly constant blood level had been established, the drug seemed to be excreted in the milk at a definite concentration per cubic centimeter rather than per total volume.

7. The total amount of sulfanilamide excreted in the milk over a period of five days was never greater than 0.23 gm., 1.6 per cent of the total dose ingested.

8. With the dosages used in these experiments, the amount of drug excreted in the milk was so small that there probably would be little danger to the nursing infant unless it was unusually susceptible to sulfanilamide.

The sulfanilamide (prontolin) was supplied by the Department of Medical Research of the Winthrop Chemical Co., Inc.

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**Smith, Earl C.: The Use of Camphor-In-Oil to Check Lactation,** New Orleans Med. Surg. J. **91:** 127, 1938.

The author has used intramuscular injections of 3 gr. of camphor-in-oil to check lactation, when indicated, in 115 patients. When the patients were started on this treatment within the first twenty-four hours post partum, 85 to 95 per cent did not develop second degree engorgement. Even after the first twenty-four hours, the usual length of time that a woman suffers from ''increased mammary tension'' is shortened. No unfavorable reactions were noted. Smith advises injections twice daily for the first two days and once on succeeding days. His average total dosage per patient was 5.1 or 16 gr.

EUGENE S. AUER.

# A PRELIMINARY REPORT ON THE USE OF SULFANILAMIDE IN PUERPERAL AND POSTABORTAL INFECTIONS*

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FOLLOWING Domagk's[1] demonstration of the bactericidal effects of the azo-sulfamido compounds in the treatment of hemolytic streptococcus infections in mice, Levaditi and Vaisman[2] and Trefouel and others,[3] of France also demonstrated their effectiveness in experiments on mice. In their researches they stressed the prophylactic rather than the curative value. Then followed the work of LaComme[4] who used the drug prophylactically giving it with satisfactory results to patients the day following delivery. Colebrook and Kenny in 1936[5] and Colebrook and Purdie[6] in 1937 reported on their use of prontosil and sulfanilamide in the treatment of hemolytic streptococcus puerperal infection with striking results. Early in its use sulfanilamide was thought to be of value only in beta hemolytic streptococcus infections, but more recent work has demonstrated its value in infections caused by other organisms such as gonococci,[7] meningococci,[8] organisms commonly found in infections of the urinary tract,[9, 10] pneumococci,[11] staphylococci[12] and *Bacillus welchii.*[13]

In order to achieve its full bactericidal effect sulfanilamide must be given early in sufficient amounts to create a concentration of approximately 10 mg. per 100 c.c. of blood. Long and Bliss[14] have demonstrated that this amount is effective. To establish this concentration it is recommended that approximately 1 gm. per 20 pounds of body weight be given in twenty-four hours, although occasionally in fulminating infections larger doses may be used. Sulfanilamide is absorbed from the gastrointestinal tract in approximately four hours, and it then passes readily from the blood stream and is widely distributed throughout the tissues. In the administration of daily divided doses of the drug an average of two to three days is required to establish an equilibrium between the amount ingested and the amount excreted in the urine; a similar interval is necessary to free the body of the substance. It is excreted practically entirely in the urine in a free state and in a conjugated form (probably as para-acetyl-aminobenzenesulfonamide).[15] In cases of impaired renal function caution must be used in the administration of sulfanilamide in order to avoid too high a blood concentration. Subcutaneous administration does not lead to a higher concentration in the blood than the oral administration, and it has seemed to us that the latter method is preferable. If this is impossible due to nausea or vomiting or the inability of

the patient to take anything by mouth, sulfanilamide administered sub-
cutaneously or prontosil solution intramuscularly may be employed.
Sulfanilamide can also be administered per rectum if necessary, although
we have had no occasion to do so. Sulfanilamide is relatively insoluble,
but an 0.8 per cent solution in normal saline can be made up and given
by hypodermoclysis when necessary. This solution is administered soon
after preparation because of its tendency to crystallize below 37° C.[14]

The question of dosage is difficult to outline rigidly and should depend
upon the clinical condition of the patient. Our practice is to continue
the original dosage until a definite improvement in the patient's condi-
tion has been noted. In most cases we have given 90 gr. per day for at
least three days, and at the end of this time the dosage is reduced to 60
gr. per day if the patient has shown improvement. As improvement con-
tinues it is reduced to 30 gr. daily. It should not be discontinued before
the temperature has been normal unless complications result. We have
found it possible to continue this dose for three to four weeks if neces-
sary. In order to combat the possibility of acidosis due to the sulfanil-
amide, we concurrently administer sodium bicarbonate 10 to 20 gr.

Since sulfanilamide has been found to be of value in numerous infec-
tions besides those caused by the hemolytic streptococcus, we have treated
every alternate case of puerperal and postabortal infection with sulfanil-
amide and have used the nontreated cases as controls. On admission
cervical cultures were taken in all cases.

In this study puerperal infection will be considered as an acute in-
fection of the female generative tract producing an acute inflammation
of the uterus or its surrounding structures, peritoneum, or blood stream.
Extragenital tract infections occurring in the puerperium were not in-
cluded in this series. All patients treated were in the obstetric infection
ward of Cook County Hospital having been delivered in the hospital or
elsewhere. Every case of morbidity having a temperature of 100.4° F.
on two occasions or 101° F. on one occasion after the first twenty-four
hours was included, and a similar temperature elevation was used in the
case of postabortal infections. The modern accepted conservative treat-
ment of puerperal infection was carried out in all cases and blood trans-
fusions were freely resorted to where indicated. The patients treated
with sulfanilamide were given this drug in addition to the above
measures.

Tables I to VII summarize our results. We have classified the various
infections into four types on a clinicopathologic basis similar to the
classification of Colebrook.[12]

> Type I:   In which the infection is limited to the uterus, vagina
>           or perineum
> Type II:  In which the infection involves the pelvic cellular tis-
>           sues, tubes, pelvic peritoneum or veins
> Type III: Associated with a generalized peritonitis
> Type IV:  Associated with a septicemia

All cases of puerperal infection and postabortal infection should be
considered as serious, but to aid in describing them we have further

classified the cases into severe and mild. We describe a severe case as one in which the patient has a fever for eight days or more or 102° F. on two days or more.

TABLE I

| Puerperal infection cases | 105 | Control | 55 | Sulfanilamide | 50 | W-40 | C-65 |
|---|---|---|---|---|---|---|---|
| Postabortal cases | 99 | Control | 52 | Sulfanilamide | 47 | W-69 | C-30 |
| Total | 204 | | 107 | | 97 | | |

TABLE II. TYPE I LIMITED TO THE UTERUS, VAGINA OR PERINEUM

| | CASES | MILD | SEVERE | TOTAL DAYS FEVER | AVER. DAYS FEVER | DIED | PER CENT MORTALITY |
|---|---|---|---|---|---|---|---|
| Puerperal Infection: | | | | | | | |
| Control | 48 | 35 | 13 | 353 | 9.4 | 0 | 10 |
| Sulfanilamide | 50 | 24 | 16 | 194 | 4.8 | 0 | 0 |
| Postabortal Infection: | | | | | | | |
| Control | 36 | 21 | 15 | 192 | 5.3 | 0 | 0 |
| Sulfanilamide | 31 | 14 | 17 | 203 | 6.5 | 0 | 0 |

TABLE III. TYPE II INVOLVING PELVIC CELLULAR TISSUES, TUBES, PELVIC PERITONEUM OR VEINS

| | CASES | MILD | SEVERE | TOTAL DAYS FEVER | AVER. DAYS FEVER | DIED | PER CENT MORTALITY |
|---|---|---|---|---|---|---|---|
| Puerperal Infection: | | | | | | | |
| Control | 6 | 0 | 6 | 110 | 18.0 | 0 | 0 |
| Sulfanilamide | 8 | 1 | 7 | 137 | 17.0 | 0 | 0 |
| Postabortal Infection: | | | | | | | |
| Control | 8 | 2 | 6 | 97 | 12.0 | 1 | 12.5 |
| Sulfanilamide | 12 | 1 | 11 | 107 | 8.8 | 0 | 0 |

TABLE IV. TYPE III ASSOCIATED WITH GENERALIZED PERITONITIS

| | CASES | MILD | SEVERE | TOTAL DAYS FEVER | AVER. DAYS FEVER | DIED | PER CENT MORTALITY |
|---|---|---|---|---|---|---|---|
| Puerperal Infection: | | | | | | | |
| Control | 0 | 0 | | | | | |
| Sulfanilamide | 0 | 0 | | | | | |
| Postabortal Infection: | | | | | | | |
| Control | 3 | 0 | 3 | 15 | 5.0 | 3 | 100 |
| Sulfanilamide | 2 | 0 | 2 | 37 | 18.5 | 1 | 50 |

TABLE V. TYPE IV ASSOCIATED WITH SEPTICEMIA

| | CASES | MILD | SEVERE | TOTAL DAYS FEVER | AVER. DAYS FEVER | DIED | PER CENT MORTALITY |
|---|---|---|---|---|---|---|---|
| Puerperal Infection: | | | | | | | |
| Control | 1 | 0 | 1 | 24 | 24 | 1 | 100 |
| Sulfanilamide | 2 | 0 | 2 | 48 | 24 | 2 | 100 |
| Postabortal Infection: | | | | | | | |
| Control | 5 | 0 | 5 | 91 | 18 | 3 | 60 |
| Sulfanilamide | 2 | 0 | 2 | 26 | 13 | 0 | 0 |

TABLE VI.  SUMMARY

| | | | | |
|---|---|---|---|---|
| | CONTROL | 55 CASES | 1 DEATH | MORTALITY 1.8% |
| Puerperal Infection Cases | Type I | 48 cases | Deaths 0 | |
| | Type II | 6 cases | Deaths 0 | |
| | Type III | 0 cases | Deaths 0 | |
| | Type IV | 1 case | Deaths 1 | |
| | Total | 55 | 1 | |
| | SULFANILAMIDE | 50 CASES | 2 DEATHS | MORTALITY 4% |
| Puerperal Infection Cases | Type I | 40 cases | Deaths 0 | |
| | Type II | 8 cases | Deaths 0 | |
| | Type III | 0 cases | Deaths 0 | |
| | Type IV | 2 cases | Deaths 2 | |
| | Total | 50 | 2 | |
| | CONTROL | 52 CASES | 7 DEATHS | MORTALITY 13.4% |
| Postabortal Cases | Type I | 36 cases | Deaths 0 | |
| | Type II | 8 cases | Deaths 1 | |
| | Type III | 3 cases | Deaths 3 | |
| | Type IV | 5 cases | Deaths 3 | |
| | Total | 52 | 7 | |
| | SULFANILAMIDE | 47 CASES | 1 DEATH | MORTALITY 2.1% |
| Postabortal Cases | Type I | 31 cases | Deaths 0 | |
| | Type II | 12 cases | Deaths 0 | |
| | Type III | 2 cases | Deaths 1 | |
| | Type IV | 2 cases | Deaths 0 | |
| | Total | 47 | 1 | |

TABLE VII.  SUMMARY OF MORTALITY

| | TOTAL CASES | MORTALITY | PER CENT MORTALITY |
|---|---|---|---|
| Control | | | |
| Puerperal infection | 55 | 1 | |
| Postabortal infection | 52 | 7 | |
| | 107 | 8 | 7.4% |
| Sulfanilamide | | | |
| Puerperal infection | 50 | 2 | |
| Postabortal infection | 47 | 1 | |
| | 97 | 3 | 3.09% |

COMPLICATIONS

To prevent certain toxic effects and serious consequences of the administration of this drug, close observation is necessary. Failure to exercise this attention may lead to definite ill effects. We feel that all patients receiving large doses of sulfanilamide should be hospitalized and kept under close observation. It is thought that in some instances the toxic effects are due to an idiosyncrasy[16] rather than to the drug itself. We have had no fatalities from sulfanilamide per se nor have we noted any renal or hepatic damage. Close observation of patients under treatment and familiarity with untoward reactions should permit detection of such reactions early enough to obviate serious trouble.

It is not always easy to differentiate between the mild toxic symptoms of the drug and symptoms due to the infection. The toxic effects we have observed are malaise, headache, nausea, anorexia, vertigo; these are seen frequently, but they usually pass off rapidly. Numbness and tingling of the extremities occur in a few cases and diarrhea is also observed in some instances. Fever has been reported as one of the toxic manifestations,[14] but in puerperal infection it is difficult to distinguish between a rise in temperature due to a change in the patient's condition or to the drug. When due to the drug the temperature rapidly subsides on withdrawal of medication.

Cyanosis of varying degree is observed in a large number of patients undergoing intensive treatment. Formerly it was thought to be due to sulfhemoglobinemia or methemoglobinemia,[12] but the amount of methemoglobin and sulfhemoglobin found in the blood is too small to explain the intense cyanosis, and it has been shown that it may be unaccompanied by any decrease in the oxygen carrying power of the blood. It is now thought that the cyanosis is due to the presence of an oxidation product[17] rather than to methemoglobin or sulfhemoglobin. Early in our use of sulfanilamide we discontinued it when we noted cyanosis; we do not do so for mild cases at present. Patients on sulfanilamide therapy should not be given magnesium sulfate as a laxative nor should they be given foods containing sulfur. Patients suffering from severe infections frequently become anemic, and it is difficult to determine whether the anemia is due to the infection or to the drug. When due to sulfanilamide severe headache and dizziness frequently precede the onset of anemia. Anemia which we thought probably due to sulfanilamide occurred in 3 of the 97 patients treated or slightly over 3 per cent which corresponds to the percentage reported by W. Barry Wood of Baltimore.[18]

Immediate withdrawal of the drug in cases of anemia may be sufficient in mild cases; blood transfusion is satisfactory in severe cases. A mild skin rash occurred in two of our cases. Deafness occurred in one case, but cleared upon withdrawal of the drug; to my knowledge this is the first case reported. Agranulocytosis occurred in one of our cases. A patient with a Type I postabortal infection, who was admitted on June 14, 1938 and was discharged on July 18, had a severe infection with six days of temperature of 103° F. and seven days of 101° F. before the development of agranulocytosis. Her red blood count on admission was 2,910,000; white blood count 16,100. A blood transfusion of 500 c.c. on June 21 was given for her anemia; on July 7 the blood count was Hb 60 per cent; red blood cells 3,590,000; white blood cells 1,800 with a typical agranulocytic differential count. A transfusion was given that day. The white count dropped to 450 on July 8 and another transfusion was given on July 10 with immediate white cell improvement to 3,500 which subsequently rose to normal and on discharge from the hospital her Hb was 67 per cent; red blood count 4,220,000 and white blood count 8,800.

Early mild toxic symptoms usually do not require any treatment, but they should put one on guard against more severe reactions. In all cases

of severe reactions the drug should be stopped and fluids forced since the drug is rapidly and practically completely eliminated in the urine.

It is evident that the great majority of patients with puerperal infection fall under the Type I classification. This corresponds to Colebrook's series[12] and other reports.[19] Since practically all the patients with localized infections survive, we feel that we have not had a sufficient number of cases of generalized infection to arrive at definite conclusions in this preliminary study.

Two patients from whom hemolytic streptococci were cultured on control treatment died; in none of the sulfanilamide treated patients who died were hemolytic streptococci found. We do feel, however, that sulfanilamide has reduced the number of days of fever in the Type I and II cases; it probably has prevented some of these infections from becoming generalized.

The difference in the mortality percentage between the control and the sulfanilamide group can very well be accounted for by the increased number of cases of Type III and IV in the control series. We plan to continue this work, and we hope, with a larger series of cases, to be able to arrive at more definite conclusions. We feel that if chemotherapy is to be of value, treatment should be instituted early. Also we should not expect striking results in cases with far-advanced infections or in those who are moribund on admittance. Since sulfanilamide has toxic effects which may be serious if not discovered, we feel that all patients should be under close observation.

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**Vamos and Bohm:  Action of Arsenobenzol Preparations on Fetus,** Arch. f. Dermat. u. Syph. **176:** 245, 1937.

The authors ascertained that arsphenamine can be demonstrated in the organs of the pregnant organism, in the decidual vessels and in the intervillous spaces, but not in the chorion or in the fetal organs. Since the independent defense of the fetus against a syphilitic infection is inadequate as the result of the impermeability of the chorion, it is important that energetic treatment is begun before or at the beginning of the pregnancy.

J. P. GREENHILL.

# USE OF A SULFANILAMIDE DERIVATIVE IN THE TREATMENT OF GONORRHEA IN PREGNANT AND NONPREGNANT WOMEN*

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THE work of Long[1] at Johns Hopkins on the use of sulfanilamide in the treatment of streptococcal infections and especially the results obtained by Colebrook and Kenny[2] in the use of sulfanilamide in puerperal sepsis, have stimulated widespread interest in its clinical application to various gynecologic affections.

The excellent results reported by Dees and Colston,[3] Herrold,[4] Cokinnis,[5] and others[6, 7, 8] in treating gonorrhea in males and by Carey,[9] Hageman[10] and Hoffman, Schneider, Blatt and Herrold[11] in gonorrheal vulvovaginitis of children, direct attention to the possible value of this drug in gonorrheal infections of adult women.

We determined to study its effect on various types of gonorrheal infection in adult women, evaluating its clinical results by the use of smears, gonorrheal complement-fixation tests, and the change in clinical symptoms occurring after the use of the drug.

The exact mechanism of the action of sulfanilamide and its derivatives on the gonococcus has as yet not been determined, although numerous experimental studies of that question have been conducted. The consensus of opinion seems to be that the effect on the gonococcus is one of bacteriostasis with some small degree of bactericidal action.[2, 12-14] Many believe also that a change is produced in the leucocytes rendering them more effective in overcoming the infection. However, the work of Osgood,[15] of Welch, Wentworth, and Mickle,[16] and of Coman,[17] seem to disprove this since they could demonstrate no chemotropic or opsonic changes. The work of Casper[18] has shown that culturing gonococci in media to which one of the sulfanilamide drugs has been added produces degenerative changes as shown by variations in morphology and size of the colonies produced.

Various derivatives of sulfanilamide having similar effects have been produced by combining azo dyes with the sulfanilamide grouping and by forming various complex organic salts. A discussion of the exact chemical composition and structure is obviously beyond the scope of a purely clinical report of this type and for that reason we refer those interested to other publications such as those of Domagk,[19] Levaditi and Vaisman,[20] and others.

The drugs of the sulfanilamide group are all readily and completely absorbed from the gastrointestinal tract. Following administration, sulfanilamide has been detected in the prostatic secretion,[21] cervical secretion,[22] the breast milk,[23] and the secretions of various glands.

Neoprontosil, the drug used in the majority of our cases, is the disodium salt of the combination of an Azo dye with sulfanilamide (disodium 4, sulfamido phenyl 2, Azo 7, Acetylamino 1, hydroxy-naphthalene 3, 6 disulfonate). Its pharmacologic properties are similar to those described for sulfanilamide by Brown, Bannick, and Foster,[24] Rosenthal,[25] and Barlow[26] have shown that its toxicity is lower and that it may be administered successfully to patients who previously had been unable to tolerate sulfanilamide because of severe toxic reactions.

Because of the many toxic reactions reported with sulfanilamide, it was decided to study the value of smaller doses given in interrupted courses over short periods. Osgood,[16] Herrold,[14] and Long[12] have stated that in nonfulminating infections such as gonorrhea, small doses seem to be more effective and less dangerous. Our patients were, therefore, given the drug in courses consisting of 40 gr. daily for periods of five days, in 10 gr. doses taken orally after meals and before bedtime.

These patients were from the Out-Patient Venereal Gynecological Dispensary of the Illinois Research and Educational Hospital. No attempt was made to select the cases. No patient was given the drug unless she had both positive smears and clinical evidence of gonorrhea. No local or other form of treatment was used with the sulfanilamide.

After routine urinalysis, blood pressure, and gonorrhea complement-fixation test, the patient was given the drug (in capsules or tablets of gr. v each) and told to take 40 gr. daily, 10 gr. after each meal and 10 gr. at bedtime for five days. She was told about toxic manifestations and warned to discontinue the drug if severe symptoms appeared. Alcohol and sexual activities were interdicted. Patients with Bartholinitis were given hot sitz baths.

The diagnosis was established by finding gonococci in urethral and cervical smears stained by Gram's method, almost all of which were examined by one of us; and by clinical signs and symptoms. No patient was considered cured unless all signs and symptoms of gonorrhea had cleared up and at least three consecutive negative urethral and cervical smears were obtained.

All of our cases were ambulatory, and were seen once weekly. After finishing a five-day course of treatment, the patient was examined clinically and bacteriologically at the next weekly visit. If she showed no further evidence of infection she was observed at subsequent weekly visits until a cure was definitely established. If, after one course, the patient still showed evidence of infection another course of medication was begun on the visit one week later. This procedure was followed until cure or failure was definitely established. After the patients were considered cured they were told to return to their nor-

mal mode of life and were then seen at gradually lengthened intervals for periods up to eight months. The pregnant patients were followed until six weeks to eight weeks after delivery and the condition of the baby was inquired into in each case. Thus, all patients except two or three uncooperative individuals were observed for periods ranging from three to eight months for evidences of relapse or incomplete cure.

There were 45 cases studied, of which 39 were chronic gonorrhea, 3 subacute, and 3 acute. There were 22 white women and 23 colored women in the series, and their ages ranged from 15 to 38 years. Nineteen of our patients were pregnant, the duration of pregnancy ranging at the time of treatment from the third to the ninth month and included both primiparas and multiparas. All degrees of gonorrheal involvement were present in this series, including urethral, Skene's vaginal, cervical, Bartholin's glands, parametrial and adnexal. There was one case complicated by arthritis and another by a mycotic vaginitis. Thirteen of the patients had been previously treated for variable lengths of time. Of the 45 patients treated, 44 were cured. One was improved but not cured.

As shown in Table I, 26 cases showed negative smears at the end of one week, 9 at the end of two weeks, 1 at the end of four weeks, and 1 at the end of four days. In 5 cases the exact time at which the smear became negative was not determined, because the patients failed to keep their appointments and returned three to ten weeks after taking the drug, at which time they were found negative, so that we were able to assume they had become negative in the interim.

TABLE I. TIME REQUIRED TO BECOME SMEAR NEGATIVE

| TIME REQUIRED | 4 DAYS | 1 WEEK | 2 WEEKS | 4 WEEKS | EXACT TIME UNDETERMINED | APPROX. AVERAGE TIME |
|---|---|---|---|---|---|---|
| No. of cases | 1 | 29 | 9 | 1 | 5 | 1.06 wk. |

The time required to establish complete cure varied, with the severity of the disease, the degree of involvement, the duration of infection at the time treatment began, and the individual response to neoprontosil. Our figures in this respect are longer than the time actually required for cure because of our method of observing the patient for a week following each five-day course of the drug. In general, acute cases and pregnant women with minimal involvement responded most rapidly, while chronic cases with extensive adnexal pathology responded more slowly. Eleven patients were completely cured at the end of two weeks, 6 at the end of three weeks, 8 in four weeks, 6 in five weeks, 3 in six weeks, 1 in seven weeks, 1 in eight weeks, and 2 in nine weeks. In 6 patients the exact time of cure was not determined. These figures are summarized in Table II.

TABLE II. TIME REQUIRED TO OBTAIN COMPLETE CURE

| TIME REQUIRED FOR CURE | 2 WK. | 3 WK. | 4 WK. | 5 WK. | 6 WK. | 7 WK. | 8 WK. | 9 WK. | EXACT TIME UNDETERMINED |
|---|---|---|---|---|---|---|---|---|---|
| No. of cases | 11 | 6 | 8 | 6 | 3 | 1 | 1 | 2 | 6 |

The number of five-day courses of the drug required for cure varied with the degree of involvement. Twenty patients were cured by one

course; 13 required 2 courses; 8 required 3 courses; 2 patients received 4 courses before cure was obtained; and 1 patient required 6 courses, as shown in Table III. Seventy-three per cent of our patients were cured by one- or two- or five-day courses of sulfanilamide.

TABLE III.   NUMBER OF COURSES OF SULFANILAMIDE REQUIRED FOR CURE

| NO. OF COURSES OF SULFA- NILAMIDE REQUIRED FOR CURE | 1 | 2 | 3 | 4 | 6 |
|---|---|---|---|---|---|
| No. of cases | 20 | 13 | 8 | 2 | 1 |

In general, the pregnant women responded more favorably than the nonpregnant.  In no instance was a gonorrheal puerperal sepsis noted in spite of the fact that none of the patients was under active treatment at the time of delivery.  All patients were discharged from the hospital by the tenth day.  There was no instance of renal irritation caused by the drug since none of the patients developed albuminuria or toxic symptoms.  Only one patient required treatment during lactation and in this instance no gastrointestinal disturbance was noted in the baby.

Re-appearance of signs of gonorrheal infection, such as the return of vaginal discharge or of positive smears showing a few scattered organisms, was noted in fourteen cases.  Of these, all but one admitted re-exposure with the same partner who had originally infected her. In each of these cases the patient had been showing negative smears and had been entirely free from symptoms for periods of from two to eight weeks at the time symptoms were again seen.  Because these patients admitted exposure with infected partners, because we had no supervision over our patients outside of the clinic, and because a large percentage of these women were of a type which would not obey any orders relative to sexual abstinence, we feel that we can safely regard these cases as re-infections rather than recurrences or relapses.

One patient who had repeated relapses admitted after prolonged questioning that the relapses followed soon after re-exposure with the same partner on each occasion.  In spite of several reinfections in her case, the disease remained limited to the cervix.

For comparison and as control cases the records of 27 patients treated previously by the usual routine of silver salts, douches, and urinary antiseptics were studied.  In these cases duration of treatment ranged from six weeks to twelve months with an average of five months. In many, complications such as Bartholinitis, pelvic peritonitis, and salpingitis developed during the course of treatment.  Many of these patients discontinued their visits to the clinic because of lack of improvement.  The percentage of recurrence of symptoms and positive smears in this group was high but exact figures are not available.

The results of the complement fixation tests are of interest as shown in Table IV.  This test was performed by the Illinois State Public Health Laboratory and was done in all of our cases except 6.  All these patients showed positive clinical signs of gonorrhea and had

positive smears. Yet, only 16 of them had positive complement fixation tests. The remaining 23 cases were reported negative. Of the cases which were positive, 6 showed a reversal to negative when the test was repeated within one to six months after clinical cure.

TABLE IV.    RESULTS OF COMPLEMENT FIXATION TESTS

| RESULT OF TEST | NUMBER POSITIVE (1 TO 4×) | NUMBER NEGATIVE | POS. CASES WHICH BECAME NEG. AFTER CURE |
|---|---|---|---|
| No. of cases | 16 | 23 | 6 |

So-called toxic effects occurring during administration of sulfanilamide were noted in 26 cases (57 per cent). In none of these were the manifestations severe enough to require withdrawal of the drug and no fatal or serious complications occurred in the entire series. Even the pregnant patients, one of whom received the drug about a week before term, showed no harmful effects, nor were any effects on the babies reported. The most frequent side effect noted was nausea, which varied from a mild and transitory type to a moderately severe degree, and occurred in most cases on the first day or two of administration of the drug. Vomiting on the first day or two occurred in 2 cases. Dizziness was a fairly frequent complaint and occurred either as the only symptom or associated with nausea or vomiting. One patient stated that while taking the drug she experienced "drawing pains" in both arms and legs not severe enough, however, to interfere with her housework. Another patient stated that she felt a tingling in her hands and feet; still another complained that the drug stimulated her and made her feel "jittery" and that as a result she slept poorly during the period of medication. Other effects noted included cardiac palpitation, a feeling of light-headedness, drowsiness, a tired heavy feeling, and repeated headaches.

No abnormal urinary findings or blood pressure changes were noted on routine examination in any of our cases. In a few patients blood counts and hemoglobin determinations were done before and after treatment, but no significant blood changes were noted.

Five cases of Bartholinitis occurred in this group, and all cleared up without incision. One had been incised prior to the patient's coming to us and was very tender and draining profusely when first seen. In this case, as in others, treatment consisted only of the sulfanilamide plus hot sitz baths. All five cleared up within five to ten days and each of these patients experienced relief from pain and tenderness within three days after beginning the treatment.

### DISCUSSION

Sulfanilamide, in our experience with this small series of cases, is a very effective agent in the treatment of gonorrhea in women. It seems far more rational to treat an infection by general measures than by local application of various bactericidal drugs, and it is more

applicable to the conditions of practice than artificial fever therapy which was so highly recommended at one time.

Our cases have shown that smaller doses of sulfanilamide given in interrupted courses are a very effective method of administering the drug and avoids the danger of occurrence of severe toxic reactions.

In some of our cases a change in the smear appearance of the organism was noted after they had begun to take the drug. Many or all of the organisms were found extracellularly and the gonococci tended to be arranged in isolated pairs or groups of pairs instead of the typical tetrads and clumped diplococci formations ordinarily seen. This peculiarity of the smears was also noted by Herrold[4] and by Jones.[27]

The patients seemed to follow a definite course toward cure after administration of the drug. In most cases the woman reported a marked improvement in subjective symptoms and general well being with a diminution or disappearance of the discharge on the first weekly visit after the medication. Following this the local findings gradually cleared up from week to week. In three cases, large adnexal inflammatory masses up to baseball size could be felt gradually decreasing in size on successive weekly visits and finally disappeared entirely in about four to six weeks. The disappearance of similar masses under other forms of treatment in the same length of time is of course possible, but we feel that it is relatively rare that this occurs, and we would not expect this to happen three times in such a small series under other forms of treatment.

It should be emphasized that many of our patients had been under treatment with argyrol, silver nitrate, etc., for long periods without improvement, and yet these promptly improved and were cured with from one to three courses of sulfanilamide. One patient who had been complaining of pain and swelling in her right knee reported complete relief from the arthritis even before the genital findings had disappeared.

### SUMMARY

1. Forty-five cases of gonorrhea in women have been treated with a sulfanilamide derivative (neoprontosil) in doses of 40 gr. daily in five-day courses. Cure was accomplished in all cases except one.

2. No serious toxic effects were observed with this dosage.

3. In the cases in which the infection was limited to the cervix and lower genital tract, no upward extension was observed under treatment.

4. Reinfection occurred 14 times in this series, but never while the patient was under active treatment, and always responded promptly to further medication.

No conclusions are justified from such a small group of cases. The results, however, are so uniform and so striking that we are greatly encouraged to continue with this method of treatment until a sufficient number of cases has been studied to confirm or deny its therapeutic value.

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## DISCUSSION ON PAPERS OF DRS. MORRIS AND BOMZE

DR. HARRY CULVER.—The concentration of sulfanilamide in milk as reported tonight corresponds very closely with that noted in urethral exudates under reasonably similar conditions. This concentration is usually somewhat above that found in the urine of the same patient.

Dr. Morris used what is generally considered as safe doses on hospitalized patients over a necessarily short period. Even then he had side reactions, such as anemia, sensory disturbances, gastrointestinal symptoms, etc. There is a tendency to prescribe enormous doses of this drug to all kinds of patients, even though it has been shown that there is an individual susceptibility to toxicity which cannot be anticipated.

Neoprontosil, the derivative used by Dr. Fall and his associates, has been found to be about 40 per cent less toxic than sulfanilamide. Its clinical behavior is similar but it is generally considered slightly less effective. I am in complete accord with their conservative dosage of 40 gr. of neoprontosil a day in young ambulatory patients. In general, especially when sulfanilamide is used, observation of the patient should be made more frequently than once a week. Untoward reactions may occur within the first forty-eight hours of administration and serious complications have been observed following the continuation of the drug under these circumstances. The dearth of serious side reactions in this study of Drs. Falls, Bomze and Fuerster is, however, striking and perhaps can be explained by the fact that neoprontosil was used instead of sulfanilamide.

A cure of 44 out of 45 patients suffering from acute or chronic gonorrheal infections, in from two to nine weeks, indicates a miraculous advance in the management of such infections. I believe, however, a more strict criterion of cure might show some recurrences. While three negative smears at three successive weekly examinations would ordinarily seem adequate, a provocative application after the use of sulfanilamide does sometimes result in the reversal to a positive smear.

Reappearance of symptoms and positive smears in 14 patients after exposure undoubtedly represents some reinfections, but we must not disregard the possibility of recurrence. Activation of subclinical gonorrhea by exposure to noninfected males is not unusual. It is clearly established that a subclinical or carrier state frequently results from the treatment of gonococcal infections with sulfanilamide.

Many reports have appeared during the last year or so on the results obtained in the treatment of gonorrhea with sulfanilamide and these vary from 90 per cent to 65 per cent of cures in all classes of cases. It is noteworthy that the more thorough the clinician, the lower will be his percentage of cures.

It has been shown that the high blood levels of sulfanilamide in either free or conjugated forms are not necessary for a satisfactory response and that the degree of response is therefore in no direct proportion to the blood level of sulfanilamide or to its concentration in the urine in genitourinary infections. Success has been noted with a blood level of 1.7 mg. per cent of sulfanilamide and failure with the concentration of 15 per cent of total sulfanilamide in the blood. In ordinary urological practice a maximum of 60 gr. a day preferably given in six 10 gr. doses both day and night for two days followed by 40 gr. a day for five to seven days would be considered adequate for one course. These medium doses given to patients under frequent observation may be either temporarily lowered or raised with benefit as indicated by the general condition of the patient.

While sulfanilamide has thus far proved itself, in general, to be the most active and efficient urinary antiseptic, it cannot be expected to do the impossible by being effective in the presence of foreign bodies such as stones or being active in the presence of any appreciable degree of urinary stasis. In the latter case, it has been observed that the urine can be kept bacteriostatic only as long as the individual is under the influence of the drug. Withdraw the drug and the original condition recurs. This drug acts best in an alkaline medium and ordinarily is tolerated better and gives a better response when taken with sodium bicarbonate.

For urinary tract infections of any type it has long been considered that diuresis produced by the ingestion of fluids has an important bearing on the clinical course of such infections. This procedure is sound and does not in any manner interfere with the curative action of sulfanilamide.

It might be of interest to state that studies of several patients with sulfanilamide fever in every instance have revealed the presence of a marked secondary anemia. Whether this anemia has anything to do with the production of fever or not, it is impossible to state but I think it is worth noting that these two conditions frequently accompany each other.

DR. PAUL C. BARTON.—Shortly after the first reports of the use of sulfanilamide appeared in the American literature the Council on Pharmacology accepted it but in doing so it was very careful to issue a number of cautions. The Council stated that it was necessary to observe carefully the effect on the blood because of the danger of sulfhemoglobinemia and methemoglobinemia. Dr. Morris has stated that the cyanosis is not related to sulfhemoglobinemia or methemoglobinemia. In spite of that fact, cyanosis indicates a rather serious condition and I am not sure it should be totally disregarded in using sulfanilamide.

Other warnings included the avoidance of magnesium sulfate, and the combination of sulfanilamide with other drugs on the basis that until more study had been made of its pharmacologic effect, and the pharmacologic effect of other drugs in combination with it, it is better to avoid such combination.

I can unofficially state that the Council will re-write its chapter on sulfanilamide in the next edition and the use of the drug in wider fields will be discussed. I do not think the Council will change its warnings.

We must be careful to limit the use of the term ''sulfanilamide'' to one chemical entity and not to apply it to combinations of sulfanilamide with other radicles. Neoprontosil is not the original prontosil, but both ''prontosils'' are compounds of sulfanilamide and azo dyes. There are literally hundreds of sulfanilamide and prontosil preparations which are available and which have been used clinically.

It might be well to consider a few of these derivatives. One is sulfanilamide-pyridine. Editorial comment in the *Journal of the American Medical Association* appeared within the last month and was in effect another warning. Let us be cautious until we know what it will do in pneumonia. Incidentally the journal pointed out that this drug is not undergoing the same rapid promotion that

sulfanilamide did, owing to the new food and drug law.  It is more toxic than sulfanilamide.  It may have a different therapeutic index as indicated by comparison of the physiologic dose with the toxic dose.  I do not think it holds much promise.

Another derivative is acetyl-sulfanilamide which was discussed by Dr. Hac in connection with the excretion of sulfanilamide by the mammary gland.  Acetyl-sulfanilamide is more toxic than sulfanilamide, and yet we find it as a form in which sulfanilamide is excreted.  I think we might consider the possibility that the acetyl-sulfanilamide that is administered cannot be detoxified by a simple acetylization in the body.  It may be for that reason that the preparation is more toxic.

DR. W. C. DANFORTH.—I wonder if it would not add to the value of subsequent work if blood levels were observed.  It has been suggested that a concentration in the blood of 7 to 10 mg. per 100 c.c. might be accepted as a therapeutic level.  I have heard that in the large medical services of New York they are using larger doses than we have been accustomed to use.  On the other hand, Dr. Culver stated that the blood concentration was not a matter of great importance.

DR. V. D. LESPINASSE.—Sulfanilamide can cause fever, and the physician must determine whether any fever during the course of therapy is due to the drug or to the disease.  If due to an exacerbation of the disease, the dose should be decreased; if the fever is due to the sulfanilamide, then the drug should be stopped.  The fever from sulfanilamide comes on from the third to the tenth day in the course of treatment.

Sulfanilamide is used in streptococcic infections, and often ultraviolet ray is used as an adjunct.  I have found that sulfanilamide makes the skin photosensitive, and when one uses the ultraviolet ray with it, the patient develops a marked erythema.  I have seen this condition in two cases: one with an erysipelas on the forehead, and the other with a streptococcic pneumonia; both of these patients have been treated locally with the ultraviolet lamp.

DR. BROMZE (closing).—In reply to Dr. Danforth's question about blood levels of the drug, it was found by the Mayo group, who did most of the work with neoprontosil, that even with large doses no higher levels than 3 mg. per 100 c.c. were reached.  We did not feel that it would be of value to repeat that phase of the work.

DR. HESSELTINE (closing).—Two problems were mentioned tonight, namely, gonorrheal infection and puerperal infection.  They are entirely different in their severity.  Naturally in puerperal infection which has a high mortality we are justified in taking a chance with the drug only when its use is properly indicated.  On the other hand, gonorrheal infection though it may cause damage does not produce nearly as much mortality, and hence greater caution is required in the use of the drug.

It has been our policy not to treat a patient with sulfanilamide until we know what the offending organisms are and then apply the sulfanilamide therapy only in patients where the bacterial invaders are supposedly susceptible to the drug.  We are still doing experimental work.  We have not found it of any value in the treatment of puerperal infection other than that due to *Streptococcus hemolyticus;* we are using it in gonorrheal infection.

We have changed our policy about cure in gonorrheal infection.  Formerly we relied entirely upon the smear.  We have found with the administration of sulfanilamide that this has not been reliable.  In one patient the culture was positive for fifty-one days after the smears became negative, and remained negative.

DR. MORRIS (closing).—We did not make blood concentration determinations at the Cook County Hospital because they were not being done when we started the work.

We found that in some cases fever occurred from the fifth to the ninth day after beginning the drug. It is difficult to say whether it is due to the infection or to the drug. Usually we find the temperature dropping by the fifth or sixth day and if it rises we think it may be due to the sulfanilamide.

In regard to anemia, one of our patients had taken only 60 or 70 gr. when she became very anemic. Our patients are closely watched for this complication. Colebrook, of course, recommended sulfanilamide only in hemolytic streptococcic infections. It is now used for practically everything and we are endeavoring to evaluate its effectiveness in puerperal infections due to other organisms.

# ABORTIONS IN RELATION TO VIABLE BIRTHS IN 10,609 PREGNANCIES*

## A Study Based on 4,500 Clinic Histories

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MANY authors have investigated the course and termination of pregnancies with particular regard to interruption before viability. One needs only to glance at the greatly varying estimates and dissimilar criteria for these studies to realize that we are still far from knowing what percentage of conceptions reach viability or will be wasted, either spontaneously or willfully. Not only are we uncertain as to the number and types of pregnancy wastage; but the causes which operate in bringing about spontaneous or induced abortions are to a great extent unknown.

### SOURCE AND CHARACTER OF MATERIAL

The present study is an attempt to throw further light on the above questions by examining statistically the clinical histories of a large number of women. The results represent careful researches into 4,500 consecutive histories taken between the years 1930 and 1938, at New York University College Clinic, Department of Obstetrics and Gynecology. These histories were obtained originally with no regard for special data necessary for the present investigation; hence, some of the important related facts are not always available. The patients were interviewed by several examiners, but always with a uniform technique supervised by the senior author.

The clinic is an organic part of a general dispensary located in New York City. The patients' incomes do not exceed $900 per annum if they are single, or $1,400 if married, maximums determined by the Joint Conference of New York Hospital Conference and County Medical Societies. Because of these restrictions, the economic standardization of the group under consideration was uniform.

Further particulars as to economic standardization were sought, on the basis of home rental. Figures, however, were only available in about one-half of the charts. There was also a large diversity of neighborhoods and number in each family sharing an apartment. It was therefore decided to abandon this procedure as too confusing.

Although there were small nationality groups, within the population sample here studied, who continue to speak their own language, live in a circumscribed neighborhood, cultivate each other's company and maintain their old world habits, it is conceivably true that their reactions to the questions under consideration would be uniform, and yet different from the majority of the patients. There were, however, so many nationalities and races represented in these small groups, that any information gained from their individual study would be inconclusive and misleading. It should nevertheless be stressed that there were a negligibly small number of recent immigrants among the patients.

The only racial group considered separately was that of the negro, which comprised 6.3 per cent of the total. The incidence of pregnancies and spontaneous and induced abortion was identical with that obtained for the entire group, so it was decided to include them without reservation.

Lacking complete figures on which to base a differential fertility and abortion rate, according to the occupations of the patients' husbands, or their own employment, it was estimated, by means of samplings, that two-thirds of the patients were wives of skilled or semi-skilled laborers and small business men. The remainder were preponderantly working women doing clerical or sales work, with a small scattering of waitresses and domestic workers.

As for the education of the patients, most of them had at least some high school training, with less than one-third completing secondary school.

*Definition of Terms.*—When pregnancy is carried for twenty-six weeks or more, it is here considered a viable birth. All premature deliveries and stillbirths are included.

For lack of more exact terminology, where the exciting cause of abortions is vague, unknown, or not directly due to willful interference, they are classified as spontaneous.

Abortions which are caused by instrumentation or toxic medications of hormonal or oxytocic nature are referred to as induced. Included in the medicated group are only those in which pregnancy was without a doubt proved.

*Major Findings.*—According to the above definitions, 3,216 patients of the entire group of 4,500 had 7,712 viable births, 1,681 spontaneous and 1,216 induced abortions, a total of 10,609 conceptions.

Stated in percentages, 72.7 per cent of all pregnancies reached viability; 15.8 per cent were wasted spontaneously and 11.5 per cent by induction.

The average number of viable births among the group of 3,216 parous patients was 2.4 per cent each; 1,497 of these women, or 46.5 per cent, had one or more pregnancies terminated by abortion. Of the 10,609 conceptions, 2,897, or 27.3 per cent, were terminated by abortions. Of the patients (1,497) who had abortions, the average number of abortions per patient was 1.9.

One thousand two hundred and eighty-four patients, or 28.5 per cent, of the total number of women studied, had either successfully prevented conception or were unable to become pregnant. Only 155, or 12 per cent, of these patients stated that they did not use contraceptive methods of any kind.

### COLLATERAL INFLUENCES

Some of the collateral influences which bear upon pregnancy and its termination are: (1) Economic; (2) social point of view, as shaped by state and church; (3) age; and (4) legitimacy.
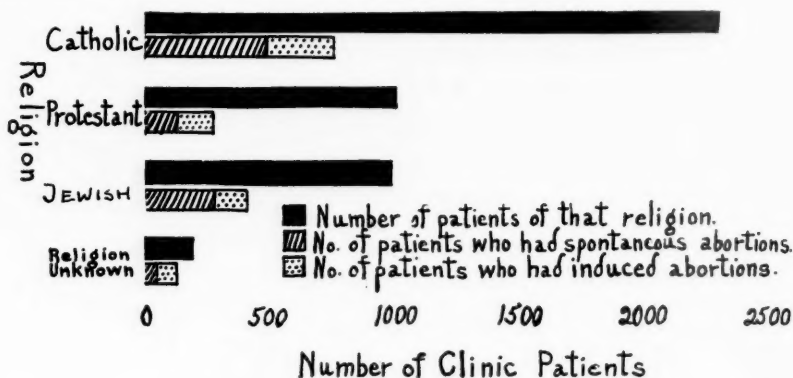


Fig. 1.—Incidence of abortion in 4,500 consecutive clinic patients, with religious affiliation. Total number who were never pregnant, 1,284 (married, 972; single, 312). Total number who had abortions, 1,497 (spontaneous, 991; induced, 574). Number of married patients who had abortions, 1,464; single patients, 33.
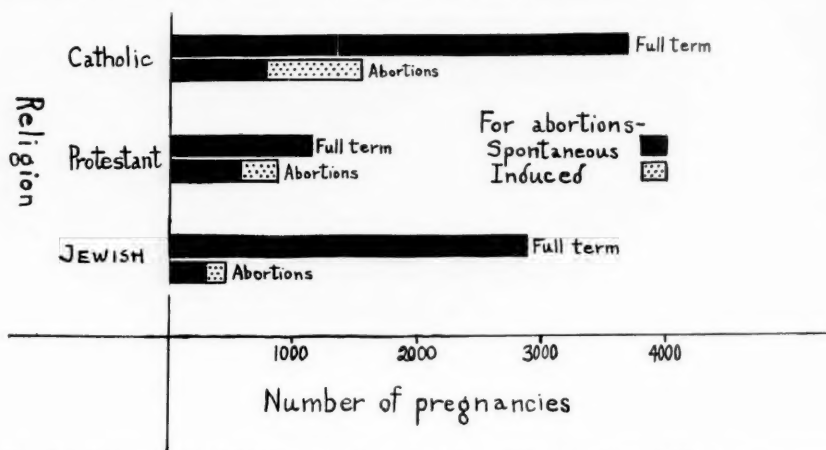


Fig. 2.—Outcome of 10,609 pregnancies: Viable, 7,712; abortions, 2,897 (spontaneous 1,681; induced, 1,216). Showing distributions among religious groups.

In the following pages a breakdown, under these headings, of the information in the clinic charts, will be given by means of tables, graphs and brief discussion.

*Economics.*—As previously stated, this is an economically homogeneous group. If light is to be thrown on the influence of family income upon the subject here under consideration, a similar study of another standardized economic group is necessary as a basis for comparison.

*State and Church.*—The state and church take very positive interest in the family and pregnancy. That the former failed to control by stringent legislation the practices of contraception and willful abortion need not be gone into at this time. Since the termination of pregnancy to a large extent depends upon the will of the patient,

it seemed to us important to investigate how much influence religious beliefs exert upon conception and abortion.   It was decided that the results of the investigation be separately expressed for the three main church groups, to ascertain if there is any variation, due to religion, within the same economic class.

Fig. 1 shows that approximately half of the group studied were Catholics.   The remainder were divided almost equally between Protestants and Jews, leaving a small and unimportant group in which the religion was not given.

This graph illustrates the fact that both spontaneous and induced abortions occur in all groups.

Theoretically there should be no appreciable difference in the frequency of spontaneous abortion among the various religious groups.   Yet approximately twice as many spontaneous abortions are recorded for Jewish as for Protestant women.   The rate for the Catholic group was only slightly lower than that for the Jewish.

One would have expected some real differences when induced abortions were studied.   However, these proved to be almost negligible.   Approximately 12 per cent of Catholic women, 14 per cent of Protestant and 13 per cent of Jewish women had had induced abortions.

More interesting figures are shown in Fig. 2, which shows that 51 per cent of Catholic women had an average of less than two children each.   Though the percentage of those who had had induced abortions was somewhat smaller than in the other groups, the number of women who had had repeated abortions was high enough to make the ratio between induced and spontaneous abortion 1 to 1.

The Protestant women had an average of approximately one viable birth each, and the ratio between viable birth and abortion was 1.3 to 1.   The relationship between spontaneous and induced abortions was about 2 to 1.

The Jewish women were the most fertile.   They averaged almost three children each, and although a large percentage of the Jewish women, as seen in this graph, had induced abortions, the total number of them was comparatively low.   The relation between spontaneous and induced abortion was similar to the Protestant group: 2 to 1.

*Age, Marriage and Termination of Pregnancy.*—The 4,500 consecutive patients, or the population group here represented, had an average age of 34 years.   The women who had children were older, an average of 35.7.   The ones who had never been pregnant were younger—30.1 years.   The average age at which marriage occurred was calculated for the parous and nonparous groups separately.   For the nonparous group it was found to be 22.5 years.   Considering the parous group: at the age of 24, 68.2 per cent of the Catholic women, 69.2 per cent of the Protestant women, and 70.7 per cent of the Jewish women were married.   The mean ages at which these three groups married were respectively 22.3, 22.5, and 22.4, an average for the whole group of 22.45 years.

The average age at the first clinic visit of parous patients was:   Catholic, 35.8 years; Protestant, 32.3 years; Jewish, 38.7 years.   Detailed age distribution is shown in Table I.

TABLE I.   PATIENTS, BY AGES, AT TIME OF FIRST CLINIC VISIT

| AGE | CATHOLIC | PROTESTANT | JEWISH | PATIENTS NEVER PREGNANT |
|---|---|---|---|---|
| Up to 24 | 293 | 170 | 69 | 492 |
| 25-29 | 233 | 138 | 71 | 260 |
| 30-34 | 289 | 105 | 105 | 204 |
| 35-39 | 347 | 66 | 117 | 112 |
| 40-44 | 234 | 71 | 101 | 84 |
| 45-49 | 179 | 43 | 98 | 31 |
| 50-54 | 94 | 6 | 29 | 54 |
| 55-59 | 22 | 20 | 33 | 35 |
| 60-64 | 7 | 8 | 22 | 11 |
| 65-69 | 10 | 4 | 5 | 1 |
| 70-74 | 24 | 0 | 0 | 0 |
| Totals | 1732 | 631 | 650 | 1284 |

Interesting figures were obtained by calculating the number of viable births oc-
curring to women of the various church groups up to and including the arbitrary
age of 30 years. These figures were arrived at by dividing the total number of
viable births up to the age of 31 by the total number of patients for the several
groups. Thus it was found that the Catholics had 1.36, the Protestants 0.82, and
the Jewish 2.26 children.
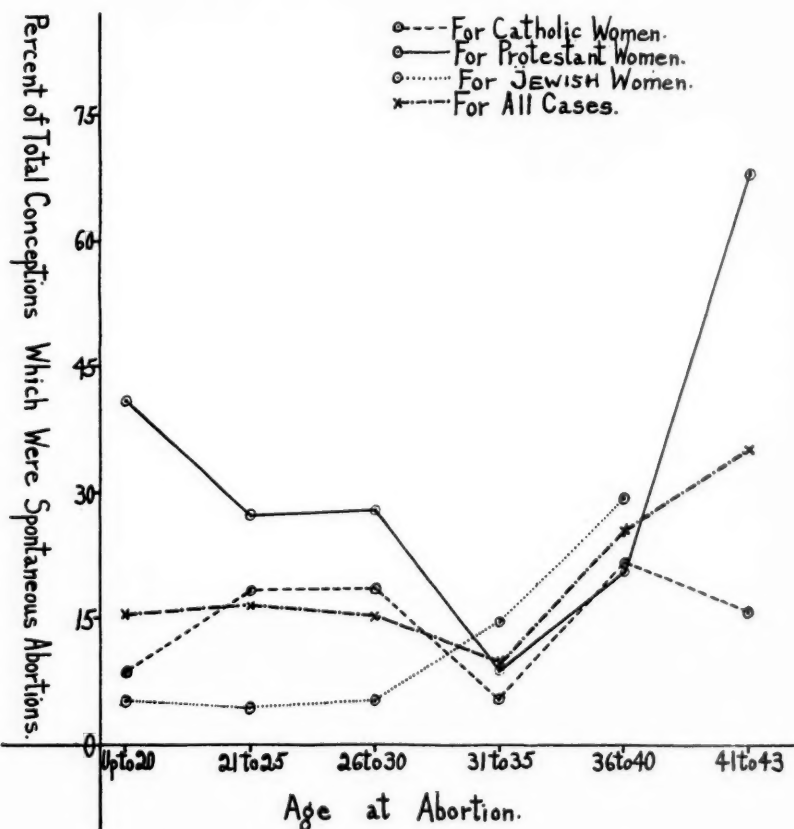


Fig. 3.—Relation of spontaneous abortion to age.

All cases considered, the mean of the pregnancies carried to viability occurred at
an average of four years following marriage. This happened regardless of at what
age the marriage took place. Table II shows that the largest number of abortions,
both spontaneous and induced, occurred around the age of 23 with a very gradual
diminution from then on.

The results separately plotted for the various church groups (see Fig. 3) show
that there was a fairly constant level of the spontaneous abortions from the early
childbearing period up to 26 years of age. From then on there was a general lower-

TABLE II.   RELATION OF ALL ABORTIONS TO AGE

| AGE AT ABORTION | UP TO 20 | 21 TO 25 | 26 TO 30 | 31 TO 35 | 36 TO 40 | 41 TO 45 |
|---|---|---|---|---|---|---|
| Spontaneous abortions | 263 | 626 | 445 | 130 | 161 | 56 |
| Induced abortions | 117 | 406 | 345 | 173 | 91 | 84 |

ing for a period of ten years, and a sharp rise thereafter.  It might be stated that between the ages of 30 and 35 fewer conceptions ended in spontaneous abortion than at any other age.  The relatively low spontaneous abortion rate for the Catholic women above the age of 40 is due to the fact that at that age the number of induced abortions in this group, as will be shown in the next graph, was approximately 80 per cent.
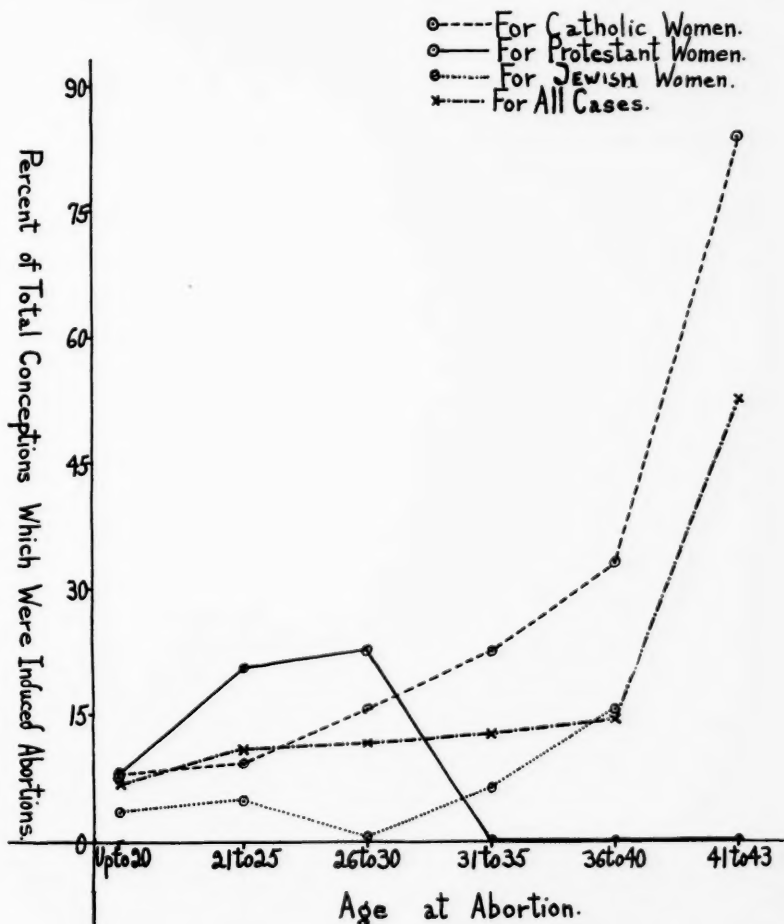


Fig. 4.—Showing relation of induced abortions to age.

Fig. 4 shows results in a companion study, demonstrating the relationship between the ages of the patients and the induced abortions.  With advancing age the percentage of induced abortions rises markedly, in both the Catholic and Jewish groups. The Protestant women have no induced abortions recorded in our charts after the age of 35.  The probable explanation is that the fertility rate is so low in this group that at this age they are willing to carry any pregnancy to its natural termination.

The distribution of conceptions according to the number of years married is shown in Table III.  In Table IV the occurrence of abortions, spontaneous and induced, respectively, is expressed in percentages.  There is a slight general rise in the spontaneous abortion rate in relation to the years married  The factor that

TABLE III. DISTRIBUTION OF CONCEPTIONS BY YEARS MARRIED

| | NUMBER OF YEARS MARRIED | | | | |
| | 0-4 | 5-9 | 10-14 | 15-19 | 20-23 |
|---|---|---|---|---|---|
| Catholic | 3094 | 1465 | 442 | 70 | 91 |
| Protestant | 1481 | 271 | 193 | 64 | 22 |
| Jewish | 1458 | 1067 | 510 | 288 | 29 |
| Totals | 6033 | 2803 | 1145 | 422 | 142 |

TABLE IV. RELATION OF NUMBER OF YEARS MARRIED, TO ABORTIONS

| | | NUMBER OF YEARS MARRIED | | | | |
| | | 0-4 | 5-9 | 10-14 | 15-19 | 20-23 |
|---|---|---|---|---|---|---|
| Percentage of | Catholic | 15.3 | 17.5 | 6.8 | 20.0 | 17.6 |
| conceptions ending | Protestant | 31.0 | 18.5 | 30.1 | 34.4 | 0 |
| in spontaneous | Jewish | 4.5 | 4.0 | 25.3 | 19.1 | 31.0 |
| abortion | For all cases | 16.5 | 12.5 | 19.0 | 21.6 | 17.6 |
| Percentage of | Catholic | 7.7 | 18.4 | 29.2 | 62.9 | 82.4 |
| conceptions ending | Protestant | 16.3 | 17.7 | 0 | 0 | 0 |
| in induced | Jewish | 4.4 | 1.1 | 7.5 | 12.5 | 69.0 |
| abortion | For all cases | 9.0 | 11.7 | 14.6 | 19.0 | 66.9 |

patients marry at various ages interferes with any significant deduction from these data. Otherwise expressed, the age of the patient might as tellingly affect the spontaneous abortion rate as does marriage and consequent pelvic trauma.

There is a steady rise in the induced abortion rate with the number of years of marriage. The conclusions are similar to those arrived at when the relation of age to induced abortion was studied.

It is striking that the desire for interruption of gestation in the older women was on the whole so prevalent. It might, however, be reasonably assumed that some of the induced abortions in these patients would have ended, if allowed to continue, in spontaneous abortions. This assumption would be particularly reasonable in those abortions which were induced by medications.

*Legitimacy.*—The question of how the legal status of marriage affected these results was next examined.

Fear of illegitimacy is said to be an important cause of induced abortions. It was found, however, that at the time of interruption there were only 33 women, among the 1,497 giving a history of induced abortion, who were not married, either at the time of abortion or of interview, a number sufficiently small so that it can be dispensed with as an unimportant force in this particular study.

*Gestation-Month of All Abortions, and Method of Induction.*—The time of gestation at which abortion took place is represented in Table V. The largest number of spontaneous abortions occurred in the third month. The largest number of induced abortions were performed in the second month of gestation.

TABLE V. GESTATION-MONTH OF ALL ABORTIONS*

| | GESTATION-MONTH | | | |
| | FIRST | SECOND | THIRD | FOURTH AND LATER |
|---|---|---|---|---|
| Spontaneous abortions | 41 | 294 | 357 | 239 |
| Induced abortions | 76 | 152 | 69 | 85 |

*The gestation-month of 744 spontaneous abortions and 840 induced abortions was not specified.

The method of induction was predominantly instrumental and 984 times a doctor was behind the instrument. Self-induction was admitted only by 103 patients. At least twelve of these were instrumental. Midwives were responsible for the abortions on only 33 women.

TABLE VI.  MORBIDITY

| | IMMEDIATE | | REMOTE | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | | CERVICITIS | | | | | |
| | CONFINED TO BED FOR FEVER AND BLEEDING | ACUTE PELVIC IN-FLAMMATION | TOTAL NUMBER | WITH LEUCORRHEA | DISPLACE-MENTS (BACKACHE) | ABDOMINAL PAIN NOT DUE TO INFECTION | ABNORMAL MENSTRUA-TION | STERILITY |
| 1216 induced abortions | 151 (12.4%) | 29 (2.46%) | 212 (17.5%) | 96 (7.9%) | 124 (10.0%) | 111 ( 9.0%) | 68 (5.5%) | 19 (1.5 %) |
| 1681 spontaneous abortions | 98 ( 5.8%) | 41 (2.4 %) | 191 (11.3%) | 133 (8.0%) | 150 ( 8.9%) | 190 (11.3%) | 105 (6.0%) | 6 (0.35%) |
| 7712 viable pregnancies | - | 38 (0.5 %) | 241 ( 3.0%) | 188 (2.4%) | 121 ( 1.5%) | 317 ( 4.0%) | 198 (2.5%) | - |

*Morbidity.*—A morbidity tabulation is attempted in Table VI. The immediate and remote after-effects are listed separately. Under immediate is classed the presence of fever, bleeding or pain requiring confinement in bed for over forty-eight hours. Among the remote consequences it was not attempted to list every possible instance, but to limit the figures to those in which, after careful investigation of the physical findings and history, we were convinced that the symptoms and diagnoses were definitely related to a here recorded birth or abortion.

## SUMMARY AND CONCLUSIONS

1. The histories of 4,500 consecutive patients attending a gynecology clinic were the basis for the foregoing study.

2. The patients belonged to groups economically and culturally similar, but socially and religiously heterogeneous.

3. The terminations of 10,609 pregnancies were analyzed, showing that: (a) 72.7 per cent of all pregnancies were carried to viability; (b) 27.3 per cent of the pregnancies ending in abortion: (1) 15.8 per cent, spontaneous, and (2) 11.5 per cent induced.

4. Of the 4,500 patients, (a) 71.5 per cent were parous; (b) of the remaining 28.5 per cent, or nonparous, 12 per cent used no contraceptive methods.

5. Of the parous group, (a) the average number of viable births per patient was 2.4; (b) 46.5 per cent had one or more pregnancies terminated by abortion; (c) the average number of abortions per patient among those with records of interrupted pregnancies was 1.9.

6. Out of the total of 4,500 patients, approximately half were Catholics, the remainder divided equally between Protestants and Jews.

7. The largest number of viable births were found among Jewish women, the smallest among the Protestant.

8. The average age when marriage took place in both parous and nonparous women, regardless of religion, was 22.45 years.

9. The mean of all viable pregnancies occurred in the fourth year of marriage.

10. Spontaneous abortion rate was highest in the Jewish group, lowest in the Protestant.

11. Induced abortion rate was approximately the same in all religious groups, an average of 12.5 per cent.

12. Both spontaneous and induced abortion rate increased with advancing age and the length of time a woman was married.

13. The incidence of pregnancies and abortions was the same in negroes and Caucasians.

14. Induced abortions were performed in the majority of cases by physicians.

15. Morbidity statistics are presented.

# MALARIA IN RELATION TO OBSTETRICS AND GYNECOLOGY

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MALARIA is both a social and a medical problem in the island of Puerto Rico, and thus constitutes also more or less of an obstetric and gynecologic problem. Being generally endemic throughout the island, it occasionally breaks out in true epidemics, in spite of the great and laudable efforts of the local Department of Health operating in conjunction with the Rockefeller Foundation in their well planned campaign for the total eradication of the disease.

A study of the relations of this disease to obstetrics and gynecology should prove interesting and enlightening to those specializing in this line of work in the island, and possibly also to obstetricians and gynecologists practicing in nonmalarial districts, or in regions where malaria has a very low incidence.

The above considerations and the fact that no report on this topic appears in our regional medical literature, has tempted me to make a survey of the literature and to summarize my personal experience in this field. The usual sources of information have afforded rather meager knowledge; the majority of textbooks and treatises on gynecology and obstetrics are very poor in their information, and a perusal of the available original medical literature shows that even this body of material, so rich in other phases of medical observation and research, is also rather weak in the discussion of this problem.

The influence that the infectious diseases produce in the normal and pathologic processes of the genital organs is a well-known and established fact. With this generally accepted dictum in mind it would be impossible to hope that the numerous and serious disturbances that malaria produces in the human organism would leave undamaged the organs of generation which are so sensitive to the systemic reactions.

The pathogenesis of malaria in relation to the female reproductive organs remains at present not well understood. In some of the cases where the process alters the glandulogerminal activity, the pathologic damage consists in the nidation of the pathogenic agent directly in the ovary with the subsequent production of a specific oophoritis, but in other instances it is the bacterial toxins or the toxins from deranged metabolic processes in the diseased organism, which act, through the agency of local nutritive disturbances or prolonged elevations of temperature.

The scientific research and evaluation of the exact and definite components of this mechanism, the true detection of the invisible originators

of the pathology present in each and every case, constitutes at present a very difficult problem because of the lack of experimental evidence.

There is no doubt that with the rapid advances in the experimental sciences and the interest that the study of malaria has recently created in the various institutions of tropical medicine, much needed light on the darkness of this question will soon come to clarify the intricacies of this problem, thus increasing its practical and theoretical importance.

Without doubt, of all the infectious diseases malaria is the one which produces the least anatomic disturbance in the female genitalia. Nevertheless, the observation, study, and research on this topic have shown that it produces sufficient functional and pathologic changes to warrant their discussion for the benefit of the general practitioner and also for the specialist not well acquainted with malarial infections.

Of these pathologic disturbances there is one which should receive noteworthy mention because it is an unusual condition which is generally misinterpreted. I refer to gangrene of the external genitalia. This condition is rare but has been observed by various students of this subject. In some cases it is found in very small patches, especially around the labia, but in others it spreads into large and alarming extensions.

It is logical to think, though it is not as yet a proved fact, that malaria, during infancy and early childhood because of the frequent and repeated relapses during this period, is liable to produce in some cases serious retardations and suspensions in the development of the genital organs.

It is well known, and this has been proved by pathologic evidence, that the infectious oophoritis is responsible for many hypoplasias and atrophies of the genitals. These constitute, without doubt, some of the cases of atrophies and hypoplasias which are found, with great surprise, during the course of gynecologic examinations, in women who are otherwise well developed and who present no evidences of endocrine disturbances or hereditary traits.

I have repeatedly observed a noticeable increase in the vaginal discharge of women suffering from chronic adnexal disease during the course of malarial attacks. I have also observed that this increase in the vaginal exudate has not the beneficial effect in the pathologic findings that we often encounter after the artificial fever produced during a course of lactotherapy. Whether this increase in the vaginal discharge is merely due to congestion and hyperemia of the pelvic organs or to some special action of this protozoon infection, I am not prepared to state at the present moment.

The functional disturbances of the ovaries are quite frequent. They are manifested by meno- and metrorrhagia if the infection is of short duration, and by amenorrhea and sterility if the process is chronic and of long standing.

When the disease appears in the premenstrual period, the menses generally start before the expected time. Whether this condition is due to the death of the ovum or to hyperemia of the pelvic organs is a question not yet definitely settled. At times the menses not only appear before the expected period, but the flow is also alarmingly

increased, especially in cases where the infection develops at the same time as the apparition of the menstruum. If the infectious process starts immediately after the end of the flow, it is not at all rare to observe a reappearance of the menses, though in some cases just the opposite occurs: a stoppage of the ovarian activity with subsequent production of amenorrhea. As a general rule, the menstrual cycle is definitely re-established in the course of time, except in those rare cases in which the ovaries have suffered irreparable damage, with development of a subsequent sterility as in the cases observed by Schaeffer.[1]

The relation of malaria to sterility is by no means a recent observation, nor is Schaeffer alone in considering it to be an established fact. Laffont[2] states that it was known in ancient times and that Hippocrates "knew of the scarce capacity of the malaric for conception" and Novak[4] also states that sterility is widely spread in regions infected with malaria.

Although these observations carry a certain authority because of the intellectual caliber of the observers and although I personally believe that no definite statement can be made until further investigations definitely settle this point, I must confess that our experience in Puerto Rico, which is an intensely malarial region, does not correspond at all to the observations of Laffont, Schaeffer, and Novak.

We have in our island a population of about 500 persons per square mile (3,400 square miles, 1,700,000 population) and a malarial incidence of 35 to 55 per cent (Earle) with no reported case of sterility which could be traced to malaria as the causative factor. Furthermore, a consideration of the above figures will convince any one, without more detailed statistics, that our fertility rate has not been appreciably weakened by the ever present endemic of malaria in the island.

Megaw's[3] statement that "During an epidemic of malaria there is usually a heavy fall in the live birth rate as well as an increase in the infant mortality" is based without doubt on the malarial production of abortion, premature birth and still birth. According to Goch[5] malaria interrupts pregnancy in 41.3 per cent of the cases. This complication is more frequent, the more advanced the gravid state of the patient. Abortion is very rarely seen during the malarial attack, it being more frequent during the intervals between the attacks, a fact which seems to indicate that the fever per se is not the principal and determining factor in the production of the interruption.

Around this interesting topic of the definite determination of the factor or factors responsible for the interruption of pregnancy, there is an extensive and rich bibliography consisting of investigations, observations and discussions, so alluring and enlightening, that we have deemed it necessary to enumerate some of the most important, so as to give a clear idea of this phase of the problem.

Runge[6] believes that although the fever is not the only cause of the intrauterine death of the fetus, it constitutes nevertheless one of its most important factors. To prove his thesis, Runge has demonstrated, through animal experimentation, that short and strong thermal stimulations of the uteri of rabbits produce tetanic contractions of this organ.

He also demonstrated that the fetuses of rabbits kept in an incubator at 41.5° C. (106.7° F.) died in utero in a very short time.

On the other hand, Seitz[7] states that the fever plays only a secondary and unimportant part, because often the pregnancy continues undisturbed despite high and prolonged elevations of temperature. This statement reminds me of a case attended at our Municipal Hospital six years ago. The patient was a multipara v, eight months pregnant, affected by *Plasmodium falciparum,* who sustained a continuous fever fluctuating between 39° and 41° C., for a period of ten days, without interruption of pregnancy or apparent injury to the vital capacity of the fetus. One month later she was normally delivered of a living, 7-pound female baby.

According to Seitz, the principal ecbolic factor lies in the circulating bacterial toxins which together with the other products of albumin disintegration excite the uterus to contractions. Thus according to his theory, the fever and the uterine contractions are nothing but the effect of the same identical cause: the bacterial toxins.

Novak also believes that the responsible factor lies in the specific substances produced by the plasmodium or else manufactured in the organism under the influence of the disease.

Lauros[8] places the blame on the occurrence of infarcts and inflammatory conditions of the placenta together with a certain peculiar and abnormal friability of the uteroplacental vessels, but these or similar pathologic changes are so frequent in processes which are not malarial in origin that the specific value of these findings is of doubtful importance.

It is hard to blame the cachexia because clinical experience has demonstrated that even the most excessive states of anemia and hyponutrition do not impede the continuation of gestation. The passage of the plasmodium from the mother to the fetus has also been suggested as an etiologic factor, but the occurrence of this transmission is so rare that it could not serve as an explanation in every case. Neither could the blame be charged to the administration of quinine, because clinical experience has taught us that untreated patients abort with greater facility than those which receive quinine therapy.

In all probability this complication is due to a combination of one or more of the factors enumerated above. Since this problem remains as yet unsolved, the exact determination of the role played by each one of them constitutes at present an important field of research.

According to Perkins,[9] Deeks "believes that eclampsia is more common in malarial districts." Laffont also believes that gravid women, affected by malaria, frequently develop eclampsia. These observations run true to our experience in the Maternity Service of our Municipal Hospital. They also correspond in some way with the newer theory of the causation of eclampsia, so well exposed by Goodall[10] who states that eclampsia is a nervous explosion more frequently found in the young, temperamental patients whose nervous system is very sensitive and unstable, not strong enough to resist rapid and intense stimulation. The increased incidence of the eclamptic episode in the gravid women

suffering from malaria should also make us think of the renal disturbances, so frequent in the course of this disease, as a possible etiologic factor.

Malaria also affects parturition. Although labor generally evolves normally, frequently a marked uterine inertia is present which prolongs considerably the first stage. I sincerely believe that many of our secondary inertias, so frequent in this region, are without doubt malarial in origin. These cases need close observation during the immediate post-partum period, because the atonia present during the course of labor is often responsible for serious post-partum hemorrhages. Some authors state that when labor starts during the febrile period, the pyrexia ceases immediately, to reappear after parturition is completed. I have observed this phenomenon only once. Involution is slow, torpid and retarded, constituting occasionally another factor in the causation of post-partum bleeding. During the puerperium, malarial relapses are common. Primary infection is not unusual. The general lowering of resistance, obstetric shock, loss of blood and energy are generally considered probable causes of the frequency of these relapses. The presence of malarial infection during the puerperium often results in a serious diagnostic problem, because the fever curves may be atypical and the plasmodium not detected in the examination of the blood. As a rule the history of previous attacks, their periodicity, the lack of visible pyogenic modifications at the genitalia, the enlargement of the spleen, a leucopenic blood count, the demonstration of the plasmodium in the erythrocytes or the favorable response to the clinical therapeusis instituted will easily clarify the obscurity of the condition.

A point which merits some consideration in the study of the relations of malaria to obstetrics and gynecology is the so-called special immunity which pregnancy has been supposed to render toward malaria. Although this theory has been denied by the majority of modern writers on this topic and although I see very little scientific basis on which the theory could be defended, I wish to report that in a detailed study made for this particular purpose of the last 300 cases in my private service at the Clinic of Dr. Pila, we found only 22 cases of malaria, and 12 of them were relapses which occurred during the puerperium.

We realize that the observation and study of such a small number of cases gives no authority to speculate on this matter, especially so when well-reputed observers as Novak and Perkins flatly deny the probability of the existence of malarial immunity in pregnancy. I must add that this group of patients belong to our upper classes, whose general health is excellent, who are surrounded by splendid sanitary conditions, and who receive strict prenatal care from the very start of gestation.

These factors undoubtedly increase their individual resistance to the disease, and in all probability play an important role in lowering the incidence. But in spite of these considerations I feel that these findings are remarkable and striking and that this question yet unsettled should serve as a splendid point for further research work.

Such an authority on the question of malarial immunity as Talia-ferro[11] states that he knows of no specific work on the relation of pregnancy to malarial immunity, but he believes from experience in his research in other lines of work, for example, in his studies on the resistance of rats to *Trypanosoma lewisi*, that this immunity, if present, might break during the latter months of gestation.

The babies born of malarial mothers show a greater mortality than those born of patients free of the plasmodium. They are generally underdeveloped, puny, and often premature. Goth states that they generally weight 339 gm. less than those born of normal mothers. Babies born of malarial mothers frequently develop malaria ten to twelve days after birth. Whether this is due to an intrauterine infection or a post-partum contact is not as yet definitely settled. Novak assures us that the placental filter is impermeable to the malarial plasmodium, but it is also well known that this filter is not always capable of resisting the entrance of pathogenic bacteria to the fetus. A great deal of ex-perimental work has recently been performed around this question and summarizing the most important findings it appears that the placenta is impermeable to the inanimate corpuscular elements, to all non-pathogenic bacteria, but that it is also liable to invasion from those bacteria which are capable of altering the placental tissue proper.

Although this paper has been prepared with the sole idea of discuss-ing the relations of malarial infections to the female genitalia, without the intention of entering extensively into the field of its treatment, there are certain aspects of these relations which have such an intimate contact with the therapy of the disease that we have been compelled by the force of these circumstances to consider briefly this most interest-ing field.

The first question to be considered is if malarial mothers should nurse their babies. This of course is a question that cannot be answered by a general rule. Each case needs for its proper and adequate solution, special study of all the factors involved. But we do know some facts and with this knowledge we are now better pre-pared to face and solve the majority of these problems. We know that quinine therapy does not alter the secretory function of the mammary gland and that it passes into the mother's milk in such small and in-appreciable quantities that it does no harm to the babies. In our island the general belief is that quinine dries the maternal secretion of milk. I believe this false idea has been created because of the fact that quinine is generally administered here with camphor in oil, which according to Mc Neile[12] and Klein[13] produces a rapid suppression of milk secretion.

Another point which merits elucidation is the use of quinine in the presence of pregnancy. Quinine is not contraindicated in the treat-ment of malaria in the presence of gestation. On the other hand, great danger may result in the injudicious avoidance of the drug. The reputation that quinine has of producing uterine contractions is greatly exaggerated as has been proved by the recent experimental work of Acton.[14] Williams[15] states that in the presence of malaria the oxytocic

properties of quinine really do not exist.    More recently another problem has arisen on the question of quinine therapy during pregnancy. According to the work of West[16] experimental and clinical evidences show that quinine given in massive doses during the gravid state produce fetal hearing defects (degeneration in the auditory nerve, spiral ganglion and peripheral neuron).

In closing, I wish to state that it is my experience that in malarial districts where relapses are so frequent during the puerperium the judicious use of small doses of quinine immediately following labor is very beneficial, because it not only prevents the probable occurrence of the relapse, but also helps a great deal in the involutional process of the genitalia.

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# STREPTOCOCCUS VIRIDANS ENDOCARDITIS IN PREGNANCY

## With Three Case Reports

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SINCE the discovery of the *Streptococcus viridans* by Schottmüller in 1909, the organism has been isolated in 15 reported cases of subacute bacterial endocarditis during pregnancy.    Among the twelve authors reporting such cases, opinion has been divided as to the management of the pregnancy, and in many instances the diagnosis has been confused with pyelonephritis or puerperal sepsis.    For these reasons it would seem worth while to present three additional case reports and to review the subject from an obstetric standpoint.

Prior to the time that Osler and Horder described the clinical aspects of this disease in 1910, there was much confusion in the terminology of endocarditis.    Acute endocarditis was thought to be quite common in pregnancy, and as early as 1856 Virchow described such a case and discussed the relationship between puerperal sepsis and "vegetative" endocarditis.    Inasmuch as puerperal sepsis was rampant at that time, many of the cases of bacterial endocarditis arising during the puerperium were undoubtedly due to the hemolytic streptococcus.    An ex-

amination of the early cases reported in the German and French literature shows that some were also due to the staphylococcus, while others were simply rheumatic lesions. It became apparent gradually that there was a chronic form of bacterial endocarditis, often of insidious onset and prolonged duration, and usually caused by the *Streptococcus viridans*. At least a dozen of the early cases were probably of this type, although the lack of bacteriologic studies makes it difficult to establish the diagnosis. An excellent review of this subject has recently been made by Jensen.[12]

This chronic form, known in Germany as endocarditis lenta, was paradoxically labeled subacute bacterial endocarditis in this country and in England. The criteria formulated by the early clinicians for establishing the diagnosis are too well known for discussion. Briefly, they include: (1) the presence of valvular lesions (or a definite history of rheumatic heart disease), (2) fever, (3) embolic manifestations, and (4) positive blood cultures.

The disease is not common in pregnancy. One case has been reported for about every 200 cases of rheumatic heart disease in pregnancy, and if heart disease occurs in 1 per cent of all obstetric patients as claimed by several authorities, then subacute bacterial endocarditis might be expected once in 200,000 cases.

For the sake of brevity, the features of particular interest to the obstetrician in all of the reported cases are summarized in tabular form.

It will be seen from the table that the disease occurred in women from 18 to 35 years of age, and that parity was not a factor. Over half of the patients gave a definite rheumatic history, although only one-third had recognized heart lesions at the beginning of pregnancy. The onset of the disease was usually in the latter half of pregnancy, and 12 of the 18 patients progressed beyond the seventh month of gestation. Of the 12 viable infants, 10 survived, while death came to all of the mothers within six months after delivery. In 11 cases the diagnosis was confirmed by autopsy.

### REPORT OF CASES

CASE 1.—A white multipara, aged 35, was first examined on April 7, 1931, during the fifth month of her pregnancy. She had had two normal deliveries at term ten and twelve years before, and two spontaneous abortions. During childhood, she was told that she had rheumatic heart disease, but there had been no symptoms of cardiac insufficiency since that time. She had typhoid fever at the age of twelve, and her appendix was removed in 1928.

The first half of her pregnancy was entirely uneventful. The initial physical examination revealed nothing unusual. The tonsils were small and not infected. The thyroid gland was not palpable. The lung fields were clear to percussion and auscultation. The cardiac rate and rhythm were normal, there were no murmurs, and the blood pressure was 110 systolic and 68 diastolic. The uterine fundus could be felt at the level of the umbilicus, and the pelvic measurements were normal. The urine contained no albumin or sugar.

Shortly after her first visit she developed a cold which persisted for three weeks. At this time a diagnosis of influenza was made, and she was kept in bed and given supportive treatment. During this illness a soft blowing systolic murmur was heard over the apex. She now developed chills and fever and a pain over the left kidney

area. A catheterized urine specimen showed numerous pus cells and many staphylococci, and a diagnosis of pyelitis was made.

She entered a private hospital on April 30, 1931, and had a bilateral lavage of the kidney pelves, with instillation of silver nitrate. The consulting urologist reported no acute cystitis, and sterile urine cultures, although the urinary sediment contained a few red blood cells, pus cells, and casts. A blood count at this time showed 72 per cent hemoglobin, a red blood count of 4,430,000, and a white cell count of 13,950 with 89 per cent polymorphonuclears.

She continued to have chills and a swinging fever. A blood culture taken on May 5 showed a growth of *Streptococcus viridans,* and a second blood count showed a slight drop in the hemoglobin and red cell count, and a slight rise in the white cell count. Examination of the heart at this time revealed a definite mitral stenosis and insufficiency. The diagnosis became subacute *Streptococcus viridans* endocarditis.

Aside from supportive treatment, the only therapy was the use of sorocin intravenously. She continued a downward course, with daily fluctuations of temperature ranging from 96 to 106° F. On May 22, 1931 (six and one-half months pregnant), spontaneous labor began, and she delivered a two pound living male fetus which survived for one and one-half hours.

The patient died on the tenth day post partum, seven weeks after the onset of her illness. Permission for autopsy was not granted.

CASE 2.—A 30-year-old white female entered the Alameda County Hospital on Jan. 28, 1937, complaining of cough and fever for the past month.

Until she was 18 years of age she had eight to ten severe attacks of tonsillitis a year, and said that she had ''mild growing pains'' during adolescence. She had two children, aged 8 and 6 years, and toward the latter part of her second pregnancy she had noticed increasing dyspnea on exertion. This subsided after the delivery, but returned about one year ago and has become progressively more severe. The shortness of breath did not interfere with her usual activities until the onset of her present illness. The remainder of her past medical history is of no significance.

Her last normal menstrual period began on Oct. 20, 1936. Moderate nausea and vomiting and slight soreness of the breasts followed, but her general health was good until one month before entry. At this time (Jan. 1, 1937) she contracted an upper respiratory infection with acute sinusitis, frontal headaches, laryngitis, and cough. Orthopnea ensued, the cough became worse, and she began to raise frothy, blood-tinged sputum. For the past two weeks there had been daily fever (up to 102° F.) and chills. One week before entry, small red spots on the wrists and painful nodules on the fingers appeared.

Examination disclosed a very pale, dyspneic and slightly cyanotic woman of average bodily build. The temperature was 100.4° F., pulse rate 120, respiratory rate 26, and blood pressure 92 systolic over 60 diastolic. On both wrists were numerous petechiae, and there were several tender nodes on the lateral aspects of the fingers. Her voice was husky, the pharynx was moderately injected, and both tonsils were enlarged and scarred. Moist râles could be heard over the bases of the lungs, and there were inspiratory wheezes. The apex beat of the heart was displaced considerably to the left and over this area could be felt a systolic thrill. The rhythm was regular and rapid, the second pulmonic sound was accentuated, and over the apical area could be heard a faint presystolic murmur. The liver edge and the spleen were just palpable, and the uterine fundus could be felt 5 cm. above the symphysis. The findings on pelvic examination were compatible with a pregnancy of three months' duration.

The hemoglobin was 54 per cent (9.12 gm.); the red blood cell count 2,750,000; white blood cell count 55,100 with 97 per cent polymorphonuclear cells, one-fourth being nonsegmented forms. Anisocytosis, poikilocytosis and occasional nucleated red blood cells were present. The blood urea nitrogen was 23 mg. per cent. The Wassermann tests were negative. The initial urine examination showed nothing abnormal.

Blood cultures were taken and after seventy-two hours showed a growth of *Streptococcus viridans.* An x-ray of the chest revealed nothing unusual in the lung

TABLE I. THE OBSTETRIC ASPECTS OF ALL REPORTED CASES OF STREPTOCOCCUS VIRIDANS ENDOCARDITIS IN PREGNANCY.

| AUTHOR | AGE | PARA | PAST HEART HISTORY | ONSET OF SYMPTOMS | TIME OF DELIVERY | TIME OF DEATH POST PARTUM | PREGNANCY TERMINATED BY | STR. VIRIDANS RECOVERED IN | FETUS |
|---|---|---|---|---|---|---|---|---|---|
| Freund[1] (1913) | 30 | ii | Rheumatic heart disease | 1 month | Undelivered | Ante partum | Undelivered | Heart blood at autopsy | Nonviable |
| Findley[2] (1921) | 30 | ii | Not stated | "Early" | 4 months | 3 weeks | Vaginal hysterotomy | Maternal blood | Nonviable |
| Walser[3] (1928) | 23 | i | Chorea and rheumatic fever | 6 months | 8½ months | 1 month | Spont. labor and delivery | Maternal blood Fetal blood | Living. Culture neg. in 1 week |
| Walser[3] (1928) | 24 | 0 | Not stated | 6 months | 7½ months | "Several months" | Spont. labor and delivery | Maternal blood Fetal blood | Died after 17 hr. (Wt. 1700 gm.) |
| Kobacker[4] (1930) | 18 | 0 | Rheumatic heart disease | 3 months | 9 months | 4 days | Cesarean section (on moribund patient) | Maternal blood Fetal blood | Living. Culture neg. in 2 weeks |
| Reid[5] (1930) | ? | v | Rheumatic heart disease | ? | 5 months | 5 months | Spont. abortion | Maternal blood | Nonviable |
| Mengert[6] (1933) | 21 | 0 | Rheumatism "Dyspnea and edema" | 6 months | 8 months | 6 months | Spont. labor, breech delivery | Maternal blood | Living |
| Mengert[6] (1933) | 27 | iv | Negative | 8 months | 9 months | 7 weeks | Spont. labor, breech delivery | Maternal blood | Living |
| Terwilliger[7] (1934) | 21 | i | Negative | 7½ months | 8½ months | Not stated | Spont. labor and delivery | Maternal blood and urine | Living. Negative cultures |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Bradford8 (1934) | 24 | i | "Heart disease" | 7 months | 9 months | 4 weeks | Spont. labor and delivery | Maternal blood | Living |
| Lieberman9 (1934) | 22 | 0 | Rheumatism in childhood | Post partum | 8 months | 6 weeks | Spont. labor and delivery | Maternal blood | Living |
| MacRae10 (1937) | 27 | 0 | Negative | 6 months | Undelivered | Ante partum | Undelivered | Maternal blood | Undelivered. (Neg. cultures at autopsy) |
| MacRae10 (1937) | 27 | iv | Chorea | "Near term" | "Near term" | Day of delivery | Cesarean section for abruptio placentae | Heart valves at autopsy | Stillborn (died from the abruptio placentae) |
| Felsen et al.11 (1937) | 25 | ? | Negative | 7½ months | 9 months | 16 days | Spont. labor and delivery | Maternal blood, throat, urine, breast milk | Living. Negative cultures |
| Jensen12 (1938) | 27 | ii | Rheumatic fever | 7 months | 8 months | 2 months | Spont. labor and delivery | Heart valves at autopsy | Living |
| Page and Campbell | 35 | ii | Rheumatic heart disease | 5 months | 6 months | 1 week | Spont. labor and delivery | Maternal blood | Died in 1 hour (Wt. 990 gm.) |
| Page and Campbell | 30 | ii | Rheumatic heart disease | 2 months | 3 months | Day of abortion | Spont. abortion | Maternal blood | Nonviable |
| Page and Campbell | 20 | 0 | Negative | 7 months | 8 months | 1 month | Spont. labor and delivery | Maternal blood | Living. Negative cultures |

fields, but showed marked cardiac enlargement with an unusually straight left border "suggestive of a mitral lesion." Daily urine examination disclosed increasing numbers of red blood cells and casts.

The patient continued to run a low grade fever and developed symptoms of congestive heart failure in spite of sedation and adequate dosage of digitalis. Therapeutic abortion was advised, but on the morning of Feb. 5, 1937 (eight days after admission), a complete spontaneous abortion occurred with minimal blood loss. Respiration became laborious, auricular fibrillation followed, and she died two hours later.

The clinical diagnosis was (1) rheumatic heart disease, mitral stenosis and regurgitation, *Streptococcus viridans* endocarditis, with congestive heart failure, and (2) three months' pregnancy with spontaneous abortion.

At autopsy the clinical impressions were confirmed. The heart weighed 450 gm. The pericardium contained 300 c.c. of clear fluid. The left ventricle was enlarged, the myocardium thickened but free from scars. The endocardium showed scarring and large, soft, granular vegetations about the mitral valve. There was marked narrowing of the mitral opening. In addition to the cardiac findings there were recent small infarcts of the right kidney cortex, a right pleural effusion, chronic passive congestion of the lungs, liver and spleen, and septic emboli to the peritoneum. The right ovary contained the corpus luteum of pregnancy. The uterus was enlarged, softened, and contained decidual fragments.

(Permission to include this case was kindly granted by Dr. Benjamin Black and Dr. J. L. Eaton.)

CASE 3.—A 20-year-old white primigravida applied for prenatal care in March, 1937, during the second month of her pregnancy. During childhood she had had bronchopneumonia three times and frequent attacks of tonsillitis, but no rheumatic or scarlet fever or other serious illnesses. The family history was of no significance.

On the initial examination no unusual findings were noted. She was a healthy girl, 5 feet 5 inches tall, weighed 117 pounds, and had a normal pulse rate and temperature. The blood pressure was 115 systolic and 60 diastolic. The heart was not enlarged to percussion, the rhythm was regular, sounds were of good quality and no murmurs were detected. The lung fields were clear. Pelvic measurements were within normal limits, and the pelvic examination revealed the usual signs of an eight weeks' pregnancy. The hemoglobin was 75 per cent (Sahli), and the blood Wassermann negative. The urine was negative for albumin and sugar, and showed no formed elements on microscopic examination.

With the exception of a moderate amount of nausea and vomiting, the prenatal course was entirely uneventful until Aug. 30, 1937 (two months from term) when she complained of a persistent dry cough. Examination disclosed a temperature of 99.4° F., pulse rate 130, respiratory rate 28, and blood pressure 110 systolic and 80 diastolic. Crackling râles could be heard over both lung fields posteriorly. A loud systolic murmur and a crescendo presystolic murmur could be heard over the entire precordium. She was put to bed and given digitalis and a cough mixture.

The cough continued unabated and she developed dyspnea, orthopnea, frequent epistaxis, and occasional blood-tinged sputum. There were night-sweats, and in the evenings her temperature was found to be 100° F. or slightly higher. A blood count on September 7 (ten days after the onset of her illness) showed the hemoglobin to be 50 per cent Sahli (a drop of 25 per cent since her first examination), 2,800,000 red blood cells, and 12,500 white blood cells with 18 per cent unsegmented forms.

A diagnosis of bacterial endocarditis was made and two blood cultures showed a delayed growth of *Streptococcus viridans,* the colonies appearing in five and seven days, respectively.

The symptoms of cough, palpitation, nausea, indigestion, orthopnea and fever continued in spite of symptomatic treatment, and she entered a private hospital on September 24. The consultants were unanimously opposed to interruption of the pregnancy at this stage, feeling that such a procedure would hardly alter the unfavorable maternal prognosis, while the chances for survival of the baby were good.

In spite of a swinging fever, the white cell count was only 8,000 with 17 per cent stab forms. Sixty grains of sulfanilamide were administered daily for four days, then discontinued for a few days because of a sulphemoglobinemia.

On September 30 (one month from term) the membranes ruptured spontaneously and labor began. Dilaudid and scopolamine were used for analgesia, and after four hours of labor, a living female child weighing 4 pounds and 13 ounces was delivered by low forceps. A blood culture was immediately taken from the umbilical cord, and no growth was reported after ten days.

During the puerperium the fever continued, now rising to 104° F. daily and becoming more sustained. Only two petechiae were noted throughout the entire illness, although they were constantly searched for. Although blood cultures continued to show the presence of virulent streptococci, no evidence of pelvic infection developed. Sulfanilamide was resumed in large daily dosages, one injection of polyvalent antistreptococcus serum was given, morphine and barbiturates were used freely, but none of the medication used appeared to have any favorable influence on the course of the disease.

The urine showed increasing amounts of albumin, and large numbers of red blood cells and casts. Repeated blood counts differed but slightly from the previous findings. The spleen or liver did not become palpable. Signs of cardiac failure appeared early, and the pulmonary congestion increased. Signs of pneumonia (or infarction?) appeared on the nineteenth post-partum day. She became irrational, deeply cyanotic, and died on November 1, one month after delivery. An autopsy was not granted.

The infant gained well and was in excellent health, but at the age of seven months died from an attack of acute enteritis.

## DISCUSSION

When subacute bacterial endocarditis complicates pregnancy, it is very frequently mistaken for pyelitis until blood cultures or beginning cardiac failure direct attention to the true diagnosis. In those cases following abortion or delivery, it is often mistaken for puerperal sepsis. With any febrile disease in the presence of rheumatic heart disease or even with the history of chorea or rheumatic fever, bacterial endocarditis must be considered, and the differential diagnosis may be readily made in most instances as soon as it is taken under consideration.

Pregnancy cannot be considered to be of any etiologic importance in the development of bacterial endocarditis, nor can it be looked upon as conferring any sort of immunity in spite of the rarity of the association. Pregnancy does, however, seem to hasten the progress of the disease, probably because of the markedly increased cardiac output which begins early in gestation, and because of the circulatory burden associated with delivery or operative intervention.

It is most remarkable, however, that out of 12 viable infants born, 10 survived and were in good health. The 2 infant deaths, moreover, were unrelated to the maternal infection, one dying of prematurity and the other being stillborn as a result of premature separation of the placenta. In two of the surviving babies, blood cultures were positive for the *Streptococcus viridans* (showing that the placenta is not a barrier to the organism), but the cultures quickly became negative. Felsen and his co-workers[11] showed that in their case the immune titer of the infant's blood was as high as that of the mother, and this fact must be of importance in explaining the ease with which these babies overcome their bacteriemia.

Since the prognosis for the mother may be considered practically hopeless, while the outlook for the fetus is excellent, it is apparent that a conservative attitude should be taken toward the pregnancy in an effort to obtain a viable infant. In the reported cases where the pregnancy proceeded to term or near term and a spontaneous delivery occurred, the average length of life following delivery was twelve weeks. In those cases where operative intervention was made or where spontaneous abortion occurred, the average length of life was six weeks post partum, showing that there is no advantage to the mother in either therapeutic abortion or operative delivery. Kobacker's[4] case in which a normal surviving infant was obtained by cesarean section on a moribund mother justifies this procedure or the performance of a post-mortem cesarean, but with this exception the obstetrician would do well to allow a spontaneous onset of labor.

Although sulfanilamide was used in Case 3 without apparent effect, Major and Leger[13] have recently reported the cure of a well-authenticated case of *Streptococcus viridans* endocarditis following the administration of sulfanilamide in large doses. Such a report would warrant the continued use of this drug.

It is also noteworthy that although streptococci are present in the blood, a localized pelvic sepsis does not occur during the puerperium, probably because of the patient's resistance to the organism. Were it not for the persistent focus on the heart valves, the septicemia might easily be overcome. In spite of the absence of uterine sepsis, the lochia has been shown to contain the streptococcus, and it need not be pointed out that the presence of such a patient on a maternity ward is hazardous, for the viridans organism has been known to produce puerperal sepsis of epidemic proportions.

### SUMMARY

There have been 15 proved cases of *Streptococcus viridans* endocarditis reported in pregnancy, to which we have added 3 case reports. The disease may be easily mistaken for pyelonephritis or puerperal sepsis at the onset but is readily differentiated by culture of the blood, examination of the heart, and careful search for embolic phenomena. While all of the mothers have died, 10 out of 12 viable infants born have survived. Transient bacteriemias in the fetus have been noted twice, but the infection is easily overcome. Interference with the pregnancy or operative delivery is not advisable, and efforts should be made to carry the fetus to viability.

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# MANAGEMENT OF BREECH DELIVERY IN MULTIPARAS

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THE subject of breech delivery in primiparas has been discussed in an article recently published,[1] and certain conclusions have been drawn from analysis of fifty years' experience with the management of this condition at the Boston Lying-in Hospital. It is of interest to present a survey of the concurrent breech deliveries in multiparas and to determine whether the conclusions drawn from the former series may be applied to the latter.

From 1888 to 1937 inclusive, among the 2,035 breech cases occurring, 560 deliveries by the pelvic route and 20 by abdominal cesarean section have been selected. All of the infants were born of multiparas at or near full term; all weighed 6 pounds or more at birth; and in all cases, except for the risks inherent in the birth process itself, the infants should have been born alive and well. Table I indicates the method of selection, the reasons for which have been discussed in previous articles.[1,2] They need not be repeated here except to state that the cases eliminated from consideration have been so treated because of evident nonviability of the infant, or because of the added fetal risks inherent in prematurity, constitutional maternal conditions dangerous to the child in utero, and such unpredictable abnormalities as placenta previa, ablatio placentae, and frank prolapse of the cord.

The stillbirths and neonatal deaths in this series are classified in two groups: those of *mechanical* and those of *intercurrent* causation. Mechanical deaths are those due to asphyxia or trauma, demonstrable clinically or at post mortem. Intercurrent deaths result either from incidental pathology of early neonatal life presumably independent of the mechanism of the birth process, or from such purely extraneous circumstances as may be specified in each given case. This type of fatality is included in the statistics to be presented, since in certain instances the question of mechanical etiology cannot entirely be ruled out.

From Table I the evidence is clear that 8.2 per cent of the 560 infants delivered through the pelvis and 10 per cent of the 20 born by abdominal section failed to survive. On the other hand, as indicated in Table II, the fatality rate has fallen from 14.5 per cent in the first 88 deliveries beginning in 1913 to 4.5 per cent in the last 200 ending with 1937. When, moreover, the deliveries from 1888 through 1912 are added to those of the last quarter-century, the recent improvement in results becomes more clearly marked as represented in Fig. 1.

Table III summarizes the results of breech delivery per vias naturales, contrasting the stillbirth and neonatal death rates before and after March 1, 1921. In our previous article we discussed the change in service policy from ''normal'' or ''assisted'' breech delivery to routine extraction under full anesthesia during the second

stage of labor, effective on the date mentioned, and outlined the reasons upon which this change of policy was based. It is of interest to note that in multiparas the stillbirth and neonatal death rate fell from 12.7 per cent before to 5.3 per cent after this date, in the case of single infants, and from 12.5 per cent to 5.1 per cent when multiple pregnancies are included. Since similar experience has led us to believe that routine extraction during the second stage is safer for the infant delivering by the breech of the primigravid woman than the classically recommended ''normal'' or ''assisted'' delivery, the above figures cannot but lead us to the same conclusion in the case of the multipara.
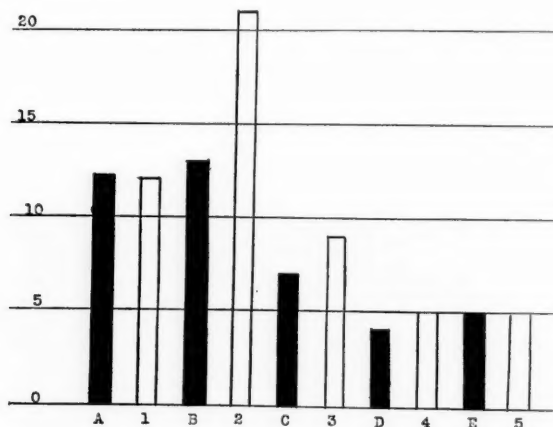


Fig. 1.—Mortality in breech delivery (1888-1937). Mature single infants. Multiparous deliveries in black and primiparous deliveries in white.

| | | | | MORT. |
|---|---|---|---|---|
| A. | 1888-1911 | 104 Deliveries | 13 Fatalities | 12.5% |
| 1. | 1888-1905 | 82 Deliveries | 10 Fatalities | 12.2% |
| B. | 1911-1921 | 100 Deliveries | 13 Fatalities | 13.0% |
| 2. | 1905-1920 | 100 Deliveries | 21 Fatalities | 21.0% |
| C. | 1921-1927 | 100 Deliveries | 7 Fatalities | 7.0% |
| 3. | 1921-1928 | 100 Deliveries | 9 Fatalities | 9.0% |
| D. | 1927-1932 | 100 Deliveries | 4 Fatalities | 4.0% |
| 4. | 1928-1932 | 100 Deliveries | 5 Fatalities | 5.0% |
| E. | 1932-1937 | 100 Deliveries | 5 Fatalities | 5.0% |
| 5. | 1932-1937 | 100 Deliveries | 5 Fatalities | 5.0% |

The 15 intercurrent deaths reported may be summarized as follows:

1. Intrauterine death during labor before admission to hospital — 4 cases
2. Sudden death of infant,
   a. 24 hours post partum, ascribed to atelectasis — 1 case
   b. 92 hours post partum, no cause assigned by autopsy — 1 case
3. Neonatal death, ascribed to atelectasis — 1 case
4. Neonatal deaths, ascribed to congenital heart disease — 3 cases
5. Neonatal deaths, ascribed to hemorrhagic disease — 3 cases
6. Neonatal deaths, ascribed to bronchopneumonia — 2 cases

It should be stressed again that without definite post-mortem evidence to the contrary it cannot be said with complete assurance that the fatalities ascribed to atelectasis, congenital heart disease, hemorrhagic disease, or even bronchopneumonia might not, in some instances, have been caused by mechanical injury to the central nervous system at the time of birth.

The 31 mechanical deaths, summarized in Table IV, are classified into groups designed to point out the method of death.

TABLE I. DELIVERIES OF BREECH PRESENTATIONS AT THE BOSTON LYING-IN HOSPITAL FROM 1888 THROUGH 1937

|  | | DELIVERIES | WELL | STILLBORN OR DIED | MORTALITY |
|---|---|---|---|---|---|
| A. Breech deliveries | (2035) | | | | |
| 1. Uncomplicated | | | | | |
| a. Primiparous | (691) | | | | |
| (1) Premature | | 102 | 45 | 57 | 55.8% |
| (2) Immature | | 89 | 77 | 12 | 13.4% |
| (3) Mature | | 500 | 449 | 51 | 10.2% |
| b. Multiparous | (768) | | | | |
| (1) Premature | | 119 | 54 | 65 | 54.6% |
| (2) Immature | | 89 | 85 | 4 | 4.5% |
| (3) Mature | | 560 | 514 | 46 | 8.2% |
| 2. Complicated | (453) | | | | |
| 3. "Nonviable" | (123) | | | | |
| (Macerated and mal-formed) | | | | | |
| B. Cesarean sections | (58) | | | | |
| 1. Uncomplicated | (52) | | | | |
| a. Primiparous | | 32 | 31 | 1 | 3.1% |
| b. Multiparous | | 20 | 18 | 2 | 10.0% |
| 2. Complicated | (6) | | | | |

TABLE II. MORTALITY IN BREECH DELIVERY. MULTIPAROUS MATURE SINGLE INFANTS (1913-1937)

|  | DELIVERIES | WELL | STILLBORN AND DIED | INC. | MECH. | MORTALITY |
|---|---|---|---|---|---|---|
| 1913    -1921(p) | 88 | 75 | 13 | 6 | 7 | 14.5% |
| 1921(p)-1927(p) | 100 | 93 | 7 | 3 | 4 | 7.0% |
| 1927(p)-1932(p) | 100 | 96 | 4 | 0 | 4 | 4.0% |
| 1932(p)-1937 | 100 | 95 | 5 | 1 | 4 | 5.0% |

TABLE III. MORTALITY IN BREECH DELIVERY, MATURE INFANTS, BEFORE AND AFTER MARCH 1, 1921

|  | DEL. | WELL | STILLBORN AND DIED | INC. | MECH. | MORT. |
|---|---|---|---|---|---|---|
| Primiparous, single | | | | | | |
| 1888—Mar. 1, 1921 | 183 | 152 | 31 | 1 | 30 | 16.9% |
| Mar. 1, 1921—1937 | 299 | 280 | 19 | 3 | 16 | 6.3% |
| | 482 | 432 | 50 | 4 | 46 | 10.4% |
| Primiparous, single and multiple | | | | | | |
| 1888—Mar. 1, 1921 | 196 | 164 | 32 | 1 | 31 | 16.3% |
| Mar. 1, 1921—1937 | 304 | 285 | 19 | 3 | 16 | 6.2% |
| | 500 | 449 | 51 | 4 | 47 | 10.2% |
| Multiparous, single | | | | | | |
| 1888—Mar. 1, 1921 | 204 | 178 | 26 | 10 | 16 | 12.7% |
| Mar. 1, 1921—1937 | 300 | 284 | 16 | 4 | 12 | 5.3% |
| | 504 | 462 | 42 | 14 | 28 | 8.3% |
| Multiparous, single and multiple | | | | | | |
| 1888—Mar. 1, 1921 | 231 | 202 | 29 | 11 | 18 | 12.5% |
| Mar. 1, 1921—1937 | 329 | 312 | 17 | 4 | 13 | 5.1% |
| | 560 | 514 | 46 | 15 | 31 | 8.2% |

Group A. Mechanically easy delivery of apparently normal infants, with death occurring a few hours to several days later, with evidences of intracranial hemorrhage.

Group B. Mechanically easy delivery, with stillbirth, or birth of a child in manifestly poor condition who cannot be revived or who dies shortly afterwards.

Group C. Mechanically difficult or traumatic delivery.

For the 8 deaths in Group A little need be said, except to comment again that this group constitutes the type of case in which the hazards of the mechanism of breech delivery per se are chiefly involved.

The cases in Group B deserve some detailed consideration.

1894. No. 4444. Sudden loss of fetal heart after admission, 2½ hours before normal breech delivery. Baby stillborn.

*1898. No. 9287. Breech delivered normally to umbilicus. Cord found pulseless. Rapid extraction done. Baby stillborn.

1907. No. 15273. Second twin. Extracted. No complications. Baby badly asphyxiated. Died in one hour.

*1908. No. 15695. Normal first stage. Breech allowed to descend. Delivery not interfered with. Expulsion rapid. Arms not extended. No difficulty with the aftercoming head. Baby stillborn.

1913. No. 20253. Second twin. Stillborn. No details supplied by record.

TABLE IV.   MECHANICAL MORTALITY IN BREECH DELIVERY

|  | GROUP A | GROUP B | GROUP C | TOTAL |
|---|---|---|---|---|
| **1888 to Mar. 1, 1921** | | | | |
| Deaths following normal or assisted delivery | 2 | 5 | 0 | 7 |
| Deaths following extraction after full dilatation | 0 | 5 | 3 | 8 |
| Deaths following extraction before full dilatation | 0 | 0 | 1 | 1 |
| Deaths following extraction after manual dilatation | 0 | 0 | 2 | 2 |
| | 2 | 10 | 6 | 18 |
| **Mar. 1, 1921 to 1937** | | | | |
| Deaths following normal or assisted delivery | 1 | 0 | 0 | 1 |
| Deaths following extraction after full dilatation | 5 | 3 | 2 | 10 |
| Deaths following extraction before full dilatation | 0 | 0 | 0 | 0 |
| Deaths following extraction after manual dilatation | 0 | 0 | 2 | 2 |
| | 6 | 3 | 4 | 13 |

*1915. No. 21702. "At time of delivery patient was unruly, and pushed buttocks of fetus out of vulva before arrival of house-officer." Arms and head easily delivered. Baby stillborn.

*1918. No. 25307. With breech on perineum delivery was effected with finger in groin. No difficulty. Baby rigid. Gasped once. Could not be revived.

*1919. No. 25821. Fully dilated over an hour. Fetal heart irregular. Both feet delivered. Arms delivered. Head delivered. No difficulty. Stillborn.

1920. No. 26867. Fetal heart disappeared twenty-two minutes before delivery. Loop of cord found compressed by left leg. Easy delivery. Baby stillborn.

**1920. No. 26899. Entered hospital three days before delivery for ante-partum hemorrhage and ? of ablatio placentae. No hemorrhage after admission. Ruptured membranes twenty-four hours before onset of labor. Fetal heart irregular from start of labor. Voorhees' bag inserted, and came out in 2¼ hours. Os fully dilated. Easy extraction. Baby stillborn.

1930. No. 2402. Extraction at full dilatation. Easy delivery. Baby in poor shape at delivery. Died seven hours. No autopsy.

1931. No. 5400. Extraction at full dilatation. Gasped on perineum. Did not breathe after delivery. Autopsy showed 50 c.c. of blood in subdural space, and a bilateral tentorial tear.

1937. No. 17698. Fetal heart disappeared twenty-one minutes before delivery. Easy extraction. Cord around neck and arm. Baby stillborn. Autopsy showed intrauterine asphyxia but no other trauma.

It is evident that 8 of these 13 cases occurred among the 231 deliveries previous to March 1, 1921, e.g., in the era of conservatism, while only 3 occurred among the 329 deliveries subsequent to the adoption of the activist policy. It seems to me, at least, that the 5 fatalities illustrated above marked with an asterisk might not have occurred had earlier extraction been instituted, whereas an early resort to abdominal delivery might have saved the case in 1920 designated with a double asterisk.

The 10 fatal cases in Group C, where delivery was frankly difficult, are summarized as follows:

In 3 instances infants weighing between 6 and 7 pounds were delivered through contracted pelves. Their deaths must be laid to misjudgment of fetopelvic relationships, although in one case the delivery was effected through an incompletely dilated cervix.

In 4 instances delivery was effected following manual dilatation of incompletely prepared cervices.

In 3 instances large infants, weighing over 9 pounds, were delivered following full dilatation. In all cases difficulty was remarked upon, and though in one the note is made, ''baby not injured in extraction,'' in the other two autopsy showed respectively vertebral and intracranial damage. The suspicion is evident that these three deaths may have been due to fetopelvic disproportion resulting from the large size of the infants.

In this study, as was the case in the primiparous series, the results of normal or assisted delivery between 1888 and 1912 might seem to indicate that conservatism was the method of choice. Table V shows that this policy resulted in only 9 stillbirths and neonatal deaths among 101 infants born, of which only 4 were definitely based on mechanical causes. Extraction, on the other hand, resulted in 6 such deaths among 35 infants born. It must be recalled, however, that during this era extraction was customary only in cases in which normal delivery had ''failed'' for one reason or another, and that the really difficult cases were all grouped under this method of management.

In brief recapitulation it should be said that experience with multiparous breech delivery at the Boston Lying-in Hospital over a period of fifty years shows mortality rates closely similar to those obtained in primiparas; in both groups the study of mortality rates and analysis of stillbirths and neonatal deaths which have occurred give strong support to the conclusion that routine extraction of the infant under full surgical anesthesia after full dilatation of the os in relation to the breech has been attained is safer for the infant than the policy of normal or assisted delivery.

TABLE V. COMPARISON OF MORTALITY FOLLOWING BREECH ''DELIVERY'' AND BREECH ''EXTRACTION''

(1888-1912)

| | TOTAL CASES | DEATHS | INC. | MECH. | | | MORT. |
| --- | --- | --- | --- | --- | --- | --- | --- |
| | | | | GROUP A | GROUP B | GROUP C | |
| Normal or ''assisted'' delivery | 101 | 9 | 5 | 1 | 3 | 0 | 8.9% |
| Extraction | 35 | 6 | 0 | 0 | 1 | 5 | 17.1% |

The role of abdominal cesarean section for delivery of breech in-
fants in multiparous women is decided upon grounds which differ in
some degree from those which make this operation advisable in primip-
aras.   In the latter type of case the real question is ordinarily that of
fetopelvic, especially of cephalopelvic, disproportion, a decision which
may require both clinical and x-ray measurements for its determination
ante partum.   In the former, however, a more or less accurate guide
is presented by the history of the previous labor or labors.  Antecedent
delivery of one or more healthy full-term infants through the pelvis
gives presumptive evidence of the adequacy of the maternal structure
for delivery of her present infant by the same route; on the other hand
if the previous labors have resulted in stillborn or traumatized chil-
dren, the presumptive evidence favors the use of the abdominal route,
and both clinical measurements of the pelvis and x-ray measurements
of the fetus assume urgent importance.

The 20 abdominal sections upon multiparas at full term are summarized in Table
VI, separating them into those done before 1932 and those performed thereafter
with benefit, potential or actual, of x-ray mensuration.  In the first group of 13, 7,
or over half, were done because of previous obstetric catastrophes; 4 had had previ-
ous sections; 1 was done for ''small conjugate'' in a patient with one child living
and another stillborn following craniotomy upon a hydrocephalic infant in breech
presentation, and 1 was done in a patient forty-four years of age in the presence of
hemorrhage in the first stage of labor.  Of the 7 cesarean sections done in 1932 and
subsequently, 6 were done because of a previous section and 1 in the presence of an
obstructing dermoid cyst.  It is of interest to note that x-rays were used for fetal
measurements in only 2 of these 7 cases, as contrasted with the employment of roent-
genometry in 12 of 19 primiparous breech cesarean sections during the same period.
Two of the 20 infants obtained by section in the entire series died: one of hydro-
cephalus, and another on the eleventh day of erysipelas.

TABLE VI.  INDICATIONS FOR CESAREAN SECTION IN MULTIPAROUS BREECH DELIVERY

|  | NO. CASES | X-RAYS |
|---|---|---|
| *1899\* through 1931* | | |
| A. One or more previous stillbirths or early neonatal deaths | | |
| following previous difficult pelvic deliveries | 7 | 0 |
| B. One or more previous cesarean sections | 4 | 0 |
| C. Contracted pelvis (''small conjugate'') plus previous | | |
| craniotomy for breech and hydrocephalus | 1 | 0 |
| D. Ante-partum first stage bleeding in woman of 44 | 1 | 0 |
| *1932 through 1937* | | |
| A. One or more previous cesarean sections | 6 | 1 |
| B. Dermoid cyst in pelvis blocking labor | 1 | 1 |

*First cesarean section recorded for multiparous breech presentation was in 1899.

In this small series the conclusions are evident that fetopelvic dis-
proportion in the multiparous breech presentation at term may often
be predicated either upon the history of previous obstetric catastrophes,
or upon the previous necessity for abdominal section.   At the same
time the advisability of routine x-ray investigation is evident not only
when any suspicion of disproportion may exist—as in the case where
the baby seems overlarge—but also to avoid the distressing accident
of performing a cesarean upon a patient whose infant is grossly
malformed.

### CONCLUSIONS

1. The cases discussed in this survey have been limited to normal multiparas at or near term with infants in utero, all weighing 6 pounds or over.

2. The management of breech delivery in the multipara by abdominal cesarean section is especially to be considered in cases where previous delivery has resulted fatally for the infant, and in cases in which previous delivery has been accomplished by cesarean. Both of these obstetrically antecedent events suggest fetopelvic disproportion.

3. In selected cases, where the pelvis is clinically contracted or when the infant is deemed overlarge, x-ray measurements may suggest abdominal delivery even though the patient has previously borne one or more normal children.

4. In any case in which abdominal delivery is contemplated, it is a wise policy to use the x-ray, not only to confirm and control the size of the infant but also to detect gross skeletal abnormalities undiscovered by clinical examination.

5. If pelvic delivery is selected, the second stage of labor should be terminated by breech extraction under full anesthesia before the birth of the umbilicus, as classically recommended, has occurred.

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475 COMMONWEALTH AVENUE

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# THE RELATIONSHIP OF NERVOUS DISORDERS TO THE MENOPAUSE*

### RICHARD H. YOUNG, M.D., OMAHA, NEB.

SINCE the time of Araeteus, there has been a trend to interpret nervousness in women as a dysfunctioning of the generative organs of the body. Two thousand years ago, it was acceptable to look upon an anxiety state, with its suffocation symptoms, as due to the upward wandering of the uterus exerting pressure upon the diaphragm. However, today, behavior, even though it be nervous behavior, deserves a more comprehensive analysis than the reduction of the problem to the functioning of an organ or set of organs in the body. Human behavior is the functioning of the individual as a whole, and can never be understood or its disorders treated in terms of one part of the body.

In spite of the many factors involved in the production of nervousness in women, this common complaint is often linked with menstrual or menopausal manifestations. Too frequently, nervousness in women between the ages of thirty and forty is glibly reduced to a "premature menopause." Where the age range is between forty and fifty-five, the "menopause" offers a handy explanation, and nervousness after the age of fifty-five may be attributed to "getting over the menopause."

The relegation of nervousness to the cessation of menstruation certainly deserves careful appraisal. In this paper, the attempt will be made to discuss first, the menopause from the standpoint of the associated changes as they affect the body and the individual; second, the nervous symptomatology that occurs at the time of the menopause; third, diagnostic points that deserve consideration; and last, plans for treatment.

<div align="center">MENOPAUSE</div>

The menopause refers to the cessation of menstruation, but this manifestation is only one sign of the involutional changes that take place. From a physiologic standpoint, the cessation in follicular activity is accompanied by changes in other endocrine organs, as well. Usually the estrin content of the blood is decreased, and there is a marked increase in gonadotropic hormone, indicating an acceleration in anterior pituitary activity. Also, both hyperthyroidism and hypothyroidism occur at this time. Virilism, increased facial hair, a change in voice, atrophy of the genital tract, and obesity are associated conditions.

Besides the above-mentioned physiologic manifestations of the menopause, there are certain personality readjustments that must take place. Much has been written about the personality adjustment that comes with puberty and adolescence, but there is very little that deals with the menopause. In particular, the psychologic implications of the menopause have been neglected. If one goes back to early mythology or explores the folklore of the different cultures, women are linked with mystical powers by virtue of menstruation. Havelock Ellis has remarked that everywhere menstruative women were supposed to be possessed by spirits and charged with mysterious forces. The cessation of the menstrual flow implies a castration experience, in the sense that the woman no longer has the ability to bear children. The loss of this power, plus the loss of certain other less well-formulated forces associated with menstruation, has a definite effect upon the sexual adjustment. In an unmarried woman, the loss may be more keenly felt as a potential force that has never been utilized, being gone forever. In the last analysis, the goal towards which the libidinous feelings are directed is family formation, and any experience that influences child-bearing calls for modification of the sexual life of the woman.

With the menopause, there is usually a slow decline in the sexual pace. Frequently, this is ushered in by a temporary increase in sexual drive that precedes the menopausal changes. This increase in libido may present a difficult problem to the woman in sexual adjustment, particularly if the needs are not recognized by the husband.

Other personality changes, as irritability, apprehensiveness and aggressiveness, have been described. In some women there appears to be a definite decrease in interests or an apparent lack of driving force.

Besides the personality changes due directly to the menopause, there are certain other factors that appear at this life period which are not connected with the menopausal changes. Most women at about the age of 45 to 50 experience a change in the family life. Children, who for

years have been dependent and who have absorbed a great share of interest and affection, emancipate themselves from the family and find new love objects.   The result is that the woman again experiences a lack of satisfaction, which, without plasticity of the personality and an ability to find new interests, may make for difficulties in personal adjustment.   Other stress or strain, such as the loss of a husband, or financial reverses, is harder to meet at this time of life because the opportunity for re-establishment of security wanes with the years.

## SYMPTOMATOLOGY

The nervous symptoms that appear at the time of the menopause are of two main types, those that are minor and directly related to the menopausal changes, and the other larger group, whose relationship to the menopause is merely temporal.

The nervous symptoms most commonly related to the menopause are those of essentially vegetative origin, and include hot flushes, sweating spells, feelings of internal nervousness and palpitation.   Associated with these sensations are feelings of tenseness that express themselves in the emotional life of the individual, as apprehensiveness, irritability, swings in mood, an easy tearfulness, and an inability to meet stress and strain.   In addition to these minor symptoms, the psychosis, involutional melancholia, has been classed as a menopausal disorder by Werner and his associates.[1]   This relationship is questioned and will be discussed later.

Other nervous symptoms occur at the time of the menopause, but as has been stated, it is probable that the relationship is only temporal.

Nervous symptoms may be classed into two groups, the minor or psychoneurotic, and the major or psychotic type.

The psychoneurotic symptoms are chiefly those of a tension and anxiety type, with panicky outbursts and attending somatic symptoms, such as drawing pains in the back of the neck, tight feelings in the throat, suffocation sensations in the chest, and pounding of the heart, chiefly symptoms above the diaphragm.

The psychotic symptoms involve the individual in a more sweeping, widespread manner, causing loss of sleep, appetite, and weight.   The symptomatology varies with the class of psychosis.   Probably most prevalent are the depressive reactions, with intense feelings of sadness and hopelessness, suicidal preoccupations, and ideas of a self-condemnatory and self-depreciatory type.   Another psychotic reaction is the paranoid development, which so frequently centers about the delusion of the husband's infidelity.   Less frequent are false beliefs about the oppressive activity of neighbors.   At times, psychotic symptoms of an unrelated organic psychosis may appear at this period, with a symptomatology that includes irritability, errors in judgment, memory deficits and widespread changes in the personality makeup.

## DIAGNOSIS

Of utmost importance in psychiatric diagnosis is a careful consideration of the patient's verbatim complaints, the conditions under which

they developed, their course and the patient's adjustments to events in the past. In evaluating the minor or neurotic symptoms of the menopause, the prime query should be whether or not the patient has experienced neurotic symptoms in the past. Almost invariably, patients do not develop a neurosis for the first time in their lives after the age of forty-five. If a woman is able to go through forty-five years of her life without neurotic symptoms, she will not subsequently develop a neurosis on a psychogenic basis. Using this simple diagnostic rule, it may be said that women with a negative neurotic history who complain of minor nervous symptoms at the menopause have a symptomatology related to the associated physiologic menopausal changes. Women in this class constitute a relatively small group.

The majority of women with minor types of nervousness are patients who have been psychoneurotics for years, and have experienced an exacerbation of symptoms with the climacterium. Frank[2] and his associates state that the more nervous and more maladjusted before the menopause, the more severe the symptoms.

The major types of nervous reactions may be distinguished by their more sweeping nature, their involvement of the whole personality. This is shown by the loss of sleep and weight, and mood change and content of thought. The schizophreniac or dementia precox type of reaction can be distinguished by the oddities and incongruities in behavior that usually carry back to early adult life. The paranoid developments can be detected by the nature of the false beliefs.

Organic psychoses may simulate in early stages the minor type of menopausal nervousness. In such cases, there is usually the history of a good past performance, with freedom from neurotic traits. With the onset of nervousness and behavior change in a woman of 45 to 55 with a negative past history, an organic psychosis, due to brain disease, and particularly paresis, should be suspected. The presence of an intellectual deficit and positive spinal fluid confirms such a diagnosis. The frequency with which women in this age group, suffering from paresis, have had their nervous symptoms related to the menopause, has been commented upon by Campbell.[3]

The depressive psychoses are diagnosed by the evidence of sadness, retardation of activity, self-condemnatory thinking, loss of sleep and weight, plus the other symptoms mentioned in the section on symptomatology. The diagnosis of involutional melancholia is usually made, chiefly because the women are in the involutional period. However, involutional melancholia constitutes a very small nosologic group, and consists of those depressed reactions which are characterized by agitation, a harping hypochondriasis, and well-rutted patterns of depressive thinking. There is no more reason to class as involutional all depressions at this period than there is the anxiety states, hypertension, or any other disease that occurs at the menopause. Many of the depressions occurring at the time of the climacterium are almost exactly the same in symptomatology, even to the content of delusional beliefs, as the depressions experienced earlier in life.

## TREATMENT

Treatment must be based upon a proper diagnosis, and while it is impossible to classify the cases into diagnostic pigeon-holes, a broad classification will be attempted for the sake of formulating plans for therapy.

1. *Nervousness Due to the Vegetative Changes Associated with the Menopause.*— For some time now, there has been a wholesale use of the follicular hormone as the chief therapeutic agent in this group. The different pharmaceutical houses have assiduously circularized the medical profession with information and favorable reports of various authors. This is an attractive type of therapy because the use of any substance extracted from the gonads has a strong emotional appeal, an appeal because of implied rejuvenation effect and a veiled promise of postponement of the loss of sexual power. Several years ago there was editorial comment[4] that physicians, not to be outdone by their colleagues, demand the hormones (from the manufacturers) as rapidly as they can be separated from the tissues, blood or excreta of animals or man, and proceed to inject them into patients.

There is reason for the use of estrogenic substance, in that the estrin titer is low during the menopause, and its injection causes a decrease in the excessive amount of gonadotropic substance. However, estrin injected is expensive, quickly excreted, and the beneficial results obtained are temporary. Where a trial is given, it is necessary to use 30,000 to 50,000 units weekly, and after an initial period of intramuscular injection with relief, smaller doses may be given and the substance administered orally. Several authors have raised the question as to the possible carcinogenic action of estrogenic substance, but this is at present merely a conjecture. Unfortunately, there is a paucity of reports on the poor and complicated results of treatment with the estrogenic substance.

Other considerations for treatment must include the use of small inhibitory doses of x-ray to the pituitary, in an effort to cut down the over-activity of the anterior pituitary hormones. This treatment is without danger, and is recommended by Collins, Thomas and Menville.[5] Cold effervescent drinks offer momentary relief for the hot flushes. Belladonna alone, or in combination with ergot derivatives, has been recommended for the vegetative manifestations; and Campbell[3] has used Lugol's solution in cases which appeared to have hyperthyroid manifestations. Sedatives for this type of nervous reaction are not recommended. An excellent statement from Ehrenfest's[6] review of the subject concludes with these remarks on treatment of this type of nervousness, ''For the majority of worried, frightened and emotionally disturbed women, premenopausal or postmenopausal, a quiet, encouraging and occasionally reiterated explanation of the situation proves the most helpful and effective sedative.''

2. *Psychoneurosis with Exacerbation at the Time of the Menopause.*—In this group are the largest number of women who complain of minor types of nervousness at the menopause. For these cases, the chief therapeutic attack must be made along psychotherapeutic lines. Simple measures, such as a careful consideration of the complaints and history, a thorough examination, a complete explanation of the nature of the disorder, reassurance, a discussion of the personal, emotional and situational factors of stress and strain, with help in planning for a more satisfying existence, accomplish results with these patients that far exceed those obtained with medication. Sedative tub baths for half an hour twice a day, and massage, are better than sedative medication. Estrogenic substance is only a secondary or supplementary type of treatment, and at that, of doubtful benefit.

The anxious patient needs repeated reassurance and frank discussion of the emotional problems, frequently in the psychosexual field, that are producing the tension. In the anxious and tense woman, every effort must be made to re-establish security and to find satisfying activities and interests toward which her driving forces and energies may be directed.

3. *Depressive Psychoses.*—The patient with a depressive psychosis that occurs at the time of the menopause should first of all be hospitalized. A depressed patient is unable to meet the ordinary life situations, and becomes increasingly more depressed and frequently commits suicide. Werner and his associates[1] have presented a strong claim for the treatment of depressions during the involutional period with theelin. However, this work has not been confirmed.

In our practice, the prognosis of the depressive reactions has been improved and the period of hospitalization immeasurably shortened by the use of the metrazol treatment, which was first utilized in cases of the schizophrenic psychosis. Dr. G. A. Young and I reported our results with metrazol in the depressions at the A. M. A. last June,[7] and subsequent experience has re-enforced our favorable impression of this type of treatment. We have treated 14 women with depressions, with an age range of from 40 to 60, with the complete recovery of 78 per cent, the improvement of 22 per cent, and failure with the treatment in none.

The convulsive treatment, while disturbing to the patients, shortens the course of treatment from months to weeks. The average treatment period is about three weeks. An additional short period is necessary for psychotherapeutic work and stabilization of the good feelings.

4. *Paranoid Developments.*—Treatment of such disorders is along psychiatric lines with the patient hospitalized. Insulin and metrazol have become valuable adjuncts to the older psychotherapeutic methods.

5. *Organic Psychoses.*—Again hospitalization is required with treatment depending upon the type of organic disease present.

## COMMENT

In this article, an attempt has been made to draw attention to the menopausal period as one of importance in the life history of the individual. Changes occur at this time that have profound influence at both the physiologic and the higher psychic, or psychobiologic levels of functioning. The changes in functioning produce effects that influence the functioning of the parts and the functioning of the body as a whole. One of the symptoms of change is a type of symptomatology that can be classed as "nervousness." In the evaluation of this complaint, it is necessary to view the total complaint picture and to study thoroughly the situation in which it developed. Care must be taken to discover whether or not the nervous symptoms are of recent origin, long-standing in nature, or an exacerbation of former neurotic difficulties.

From a diagnostic standpoint, it must be decided whether nervousness is major or minor in type and how much of the symptomatology is due to the physiologic change of the menopause, and how much might be attributed to other factors, physical, situational and emotional.

Treatment must be along broad lines which take into consideration all the facts in any given case. Such a plan will include, when indicated, the use of drugs whose effect is chiefly upon the vegetative nervous system, administration of endocrine products, situational alteration, and work with the personality problems involved.

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# PYELITIS OF PREGNANCY

## A Five-Year Study

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FROM the time of the opening of this Clinic in September, 1932, we have been impressed by the number of patients who developed pyelitis in their pregnancy, for there seemed to be many more than we had formerly been led to believe from the reports of other clinics. During this time we have conducted a thorough study into etiologic factors causing pyelitis as well as the clinical aspects of the disease; most of the details of our work have been previously reported and are available in the literature. However, as there is a dearth of information with regard to the sequelae of pyelitis it seems wise that we should report our later findings in patients studied. The only sizable report of this nature in the English language came from the Boston Lying-in Hospital a number of years ago, and much of its information was based on older methods of study. We wish, therefore, to add somewhat to the knowledge of this aspect of the problem by reporting what our results have been from September, 1932, to September, 1937.

During this time there occurred 168 cases of proved pyelitis in a total of 14,000 deliveries. Many more than this number of case histories were studied but all others were discarded because of insufficient evidence of definite pyelitis. This gives us an incidence of 1.2 per cent for pyelitis of pregnancy, whether ante partum, intra partum or post partum. These 168 cases occurred in 164 patients as 4 patients had two attacks during this period of study.

This residual group of 168 was subdivided into those who developed their pyelitis during the ante-partum period with or without a subsequent post-partum flare-up, those who developed a pyelitis during labor, and those who developed it during the post-partum period. There were 98 cases of ante-partum, 62 cases of post-partum, and 8 incidences of intra-partum pyelitis. Because the latter group is so small, it has been included in the ante-partum group in coming to most of our conclusions.

We do not wish in this paper to obscure conclusions by a multiplicity of statistics but in such a study, a certain number of them is necessary, and we shall take these up as briefly as possible, discussing them fully whenever plausible.

It is commonly stated that pyelitis is more common in primigravidas than in multigravidas. In this series there seems to be no particular predilection in either group, for of the 98 ante-partum patients, 46 were primigravidas and 52 multigravidas, in the 62 post-partum patients, 34 were primigravidas and 28 multigravidas, and in the 8 intra-partum patients, 2 were primigravidas and 6 multigravidas.

Students of this disease have been much interested in its clinical aspects in an effort to find the best way to explain recurrent acute exacerbations and some have gone so far as to say that pyelitis in childhood is important in this respect.  Our study does not add impressive weight to this point of view as only 12, or 10 per cent, gave a past history of pyelitis.  Three of these had had a previous attack of pyelitis in this hospital during the time of study.  Four only were primigravidas and gave a history of pyelitis in childhood or prior to the onset of a pregnancy.  In the post-partum group, 5 had had a previous history of pyelitis, one in a former pregnancy, and the other 4 prior to the onset of their first pregnancy.

So little has been done to correlate pyelitis in infancy and childhood with pyelitis in pregnancy that it is practically impossible to recognize earlier infection as a factor in later attacks.  A small group of children with pyelitis has been followed by Wharton, Gray and Guild, and their results are published in the *Journal of the American Medical Association* (109: 1597, 1937).  Their report reveals that 57 per cent of these children had abnormal urinary tract findings in adult life, only two became pregnant, and one of these developed pyelitis.  However, the series is too small to draw any conclusions as to the effect of childhood pyelitis upon the kidneys during pregnancy.

DeLee emphasizes the increased incidence of pyelitis in patients suffering from toxemia while Bear and others have noticed a decreased occurrence.  The incidence of toxemia in our clinic population is about 10 per cent which corresponds almost exactly with that of toxemia associated with ante-partum pyelitis.  On the other hand, in the puerperium, 24 per cent of the patients who developed pyelitis had developed a toxemia of pregnancy during the ante-partum course.  This great increase in the latter percentage as contrasted with the ante-partum group is at first quite startling, but on closer study of the 15 patients with toxemia who developed post-partum pyelitis, it was established that in 7 of them the attack of pyelitis immediately followed the kidney function test performed after delivery.  In explanation it should be stated that in this clinic, the urea clearance test and fractional phenolsulphonephthalein test are done on the same day in the post-partum period, necessitating the use of an indwelling catheter for a period of from four to five hours.  The microscopic study of the urine at the time of the first test was negative, but several days later when the second test was performed the microscopic urine usually contained a definite number of white blood cells and within two or three days of the second test, pyelitis developed.  While not conclusive, we feel that this is very suggestive evidence that 7 of these 15 patients were infected at the time of the kidney function test, and if these 7 are eliminated the incidence of toxemia among the post-partum pyelitis group falls to about the incidence of toxemia for the whole clinic.  Our study, therefore, fails to substantiate the point of view of those who feel that there is an intimate relationship between toxemia of pregnancy and pyelitis.

Of the 98 ante-partum patients, 20 were not sufficiently worked up or refused to return for investigation, and consequently cannot be used

in the detailed part of the study. Of the remaining 78, 33 patients had a subsequent pregnancy in this hospital and four of these subsequently pregnant patients had a recurrence of their pyelitis, 8 had positive cultures from the ureters but no recurrence, 21 had negative cultures. Of the 62 patients who developed pyelitis post partum, 4 had subsequent pregnancies, and of these 4, one had a recurrence in a post-partum period subsequent to pregnancy, and 3 had negative cultures and no recurrence.

The incidence of a subsequent attack in the patients adequately treated is small, 5 in 168 cases. We cannot emphasize too strongly the importance of regular follow-up on patients who have had pyelitis until 3 cultures at monthly intervals are found to be negative. Most of our patients were treated by conservative methods and by cystoscopy though mandelic acid was used in a small group, and in the last year, sulfanilamide. The results of these two methods of treatment will be reported later when the series are sufficiently large.

A subsequent pregnancy was discouraged until the cultures were negative for two years, and most of the patients received contraceptive advice, but needless to say many became pregnant sooner than we had hoped. It is interesting therefore to contrast those patients who were cooperative with those who failed to follow our advice, for in doing so it may be possible to gain some concept of the relationship between chronic infection and reinfection. In the case of patients who had had a severe first attack in pregnancy with residual damage, we feel that more recurrences were avoided by treatment between pregnancies and during subsequent pregnancies, even though their cultures were negative. Eight patients with positive cultures and many with negative cultures were followed through a second pregnancy by periodic cystoscopy and had no recurrence. The evidence seems to indicate that while it is desirable to obtain bacillus-free urine between pregnancies it is possible with diligent ante-partum care to guide patients having bacilluria through a subsequent pregnancy without having a flare-up of the disease. This possibility should not dull our desire to accomplish eradication of the infection because we have ample evidence to show that low grade chronic fibrosis is probably progressive in these patients as long as the infection persists.

Other studies have shown that pyelitis is essentially a disease of the third trimester of pregnancy and this is corroborated by our findings. Of the 98 patients, 60 developed pyelitis in the third trimester, 35 in the second and only 3 in the first.

It has been shown that when pyelitis develops before the sixteenth week of pregnancy, the prognosis for the patient is quite different from that which obtains when it occurs in the latter part of pregnancy. Treatment in these cases depends upon the persistence of the acute signs of the disease, the actual amount of kidney and ureteral damage and the response of the patient to therapy. Of the 10 patients developing pyelitis before the sixteenth week, 3 were necessarily treated by operative abortion and 6 were allowed to go to term. Of the latter group 4 delivered living babies and 2 dead babies. We can see no definite con-

nection between the pyelitis and the unfortunate outcome in these latter two pregnancies, because the acute pyelitis in both patients cleared up early in pregnancy, and there was no subsequent attack. However, both did continue to have positive cultures through their ante-partum courses.

In this same group of 10 patients the cultures in 2 who were allowed to go to term became negative during pregnancy; 2 others became negative within three months of the time of delivery or interruption; 3 became negative at from three to six months, and 3 became negative under twelve months. We think that it is fairly unusual for all these patients to have had negative cultures in less than twelve months, because in the remaining 88 ante-partum patients, 14 had positive cultures for longer than a year. It is possible that if the disease develops early, is recognized and treated radically, the prognosis for the patient is better from the point of view of positive or negative urine cultures.

In the whole group we attempted to correlate the time of onset of pyelitis with the duration of the fever in the acute attack and with the type of treatment in an effort to see whether the date on which the ureteral cultures became negative might depend on the time of onset or type of treatment. We divided our treatment into three groups—treatment by conservative methods only, conservative treatment plus cystoscopy, and a combination of these two forms of therapy with mandelic acid. Unfortunately in the 98 patients, only one was treated with complete conservatism, and only 7 combined all three forms. These eight are not enough from which to draw any conclusions but in the 90 patients who were treated by a combination of conservative and cystoscopic methods, there did not seem to be any correlation between the onset, type of treatment, and time the culture became negative. Of the entire 98 patients, 46 had a febrile course post partum. Yet many of these had had an afebrile interval between the acute ante-partum attack and delivery. This interval was in some cases a matter of months. Evidence would tend to show that in the presence of positive cultures but in the absence of fever, the disease is in a chronic state and is capable of producing progressive fibrosis of the ureter and kidney pelvis. A post-partum flare-up is a natural result in a large percentage of these cases but can be avoided often by periodic dilatation of the ureters following the acute attack and before delivery.

Of the 38 patients who developed pyelitis in the first two trimesters of pregnancy and were cured of their acute attack long before the onset of labor, 22 had a febrile puerperium, 11 were afebrile, 4 were delivered elsewhere, and one died. When last seen during this period of study 24 of the group of 98 ante-partum patients had positive cultures.

The fetal mortality (including both the babies born at term who died, the prematures who died, and the abortions which had to be done because of the disease or which were caused directly by the disease) in the ante-partum group of 106 patients, was 15.8 per cent. There were 4 premature or full-term babies who failed to survive whose death was directly attributable to pyelitis, and there were 13 abortions as the result of pyelitis. The abortions, of course, were performed in an effort to

preserve the health of the mother, but when we are attempting to determine the effect of pyelitis on pregnancy, they certainly must be counted as lost pregnancies for this group of patients.

As stated above, three of the abortions were done on or before the sixteenth week of pregnancy, and the remaining abortions or miscarriages were scattered between the eighteenth and the twenty-seventh week of pregnancy. It would seem that the babies of mothers suffering from pyelitis are unusually small because abortions or miscarriages performed as late as the twenty-fourth to twenty-seventh week yielded fetuses weighing only 500 to 750 gm.

There were 9 premature deliveries because of pyelitis, and of these, 3 babies failed to survive. When we add the 13 abortions and 9 prematures, we arrive at a figure of 22 failures to conceive viable offsprings in a total of 106 pregnancies, which result can be blamed directly on pyelitis. This is an effective commentary upon the results of pyelitis upon the child.

The onset of post-partum pyelitis in patients previously free of the disease occurred most frequently in the first week: 36 of 62 patients developed pyelitis at this time, 22 of these on the first day. The 7 patients whose pyelitis followed kidney function tests are not included in this group. The infection is almost always evident before the twenty-first day post partum; we had only 3 cases whose onset occurred after this time.

The explanation of the onset of pyelitis in the first week in over half of our cases is simple if one accepts the theory of lymphatic extension of the colon bacillus. It appears that in most instances pyelitis is secondary to a pre-existing infection of the lower genitourinary tract. We are of the opinion that the infection is carried from the bladder up the lymphatics of the ureter and paraureteral tissue to the kidney pelvis, and do not believe that the infection ascends the lumen of the ureter against the current of urine. In a previous study we have shown that immediately post partum, there is a relaxation and atony of the musculature of the ureters, giving a coincidental dilatation of the lymphatics which, in the presence of infection in the bladder and a lack of resistance on the part of the patient, can easily carry the colon bacillus to the kidney pelvis where it finds a ready medium for growth in the stagnant or slowly moving urine.

Additional proof of this theory of bladder infection can be given by stating that the duration of labor in our post-partum pyelitis group was about twenty-two hours as contrasted to the average duration of fourteen hours in a large group of normal multiparas and primiparas. In the 22 patients who developed pyelitis on the first day post partum, the average length of labor was twenty-two hours which means that for this period of time the bladder and lower urinary tract suffered constant impingement between the fetal head and more rigid structures of the pelvis. The high incidence of bladder infections following long labors is so well recognized as not to need further emphasis.

Reference has been made to fetal mortality. We must complete the picture by indicating the incidence of death in the mother, as a result

of pyelitis or complications in which pyelitis was a contributing factor. There was an incidence of 3.58 per cent as compared to the mortality for the clinic during this five-year period of 2.4 per thousand pregnancies or 0.24 per cent. In other words the maternal chances of death are increased 16 times by an attack of pyelitis.

The physiology of the ureter in normal pregnancy has been the subject of extended study in this clinic and has been reported in *Surgery, Gynecology and Obstetrics*. To summarize very briefly, it was found that the ureter which had normal peristalsis and tone until the fourth month began to lose these functions gradually and by the sixth month the peristalsis and tone had practically disappeared. They returned again in the last month of pregnancy, were lost post partum, and finally became normal again about the time of the six-weeks' visit. The loss and recovery of function followed very closely the dilatation of the ureter and its return to normal size.

Parallel to this investigation of normally pregnant patients, many tracings on patients in various stages of pyelitis of pregnancy were also made. Several interesting facts concerning the function of the ureter in the presence of an infection were brought out in this way.

In the early acute phases of the disease, there is a definite increase in peristalsis and tone. We noted this same reaction in a nonpregnant patient with negative cultures but with a definite stricture of the lower end of the ureter. Absence of peristalsis and tone was generally observed in the last stages of the acute attack and persisted as long as the cultures remained positive. There seemed to be no definite relationship between dilatation of the ureter and lack of peristalsis in the infected patient. On the other hand, patients who had suffered pyelitis in a previous pregnancy showed no constant amount of peristalsis or tone in a subsequent pregnancy, regardless of whether the cultures were positive or negative.

It would, therefore, seem that tracings of ureteral activity might be the best indication of the extent of ureteral damage, since these are a direct graphic record of the contractility of the muscle fibers of the ureter and kidney pelvis. We frequently observed a lack of peristalsis and tone in one patient who had had a previous pyelitis while another would have normal function, the cultures in both cases being negative and the clinical course during the previous attack being more or less identical. This can be explained only by assuming that one patient had a greater degree of fibrosis in the ureter than the other and consequently poorer peristaltic function. A patient with fibrosis of the ureter and the associated inflammatory strictures has a greater chance for reinfection in a subsequent pregnancy, yet it is difficult to determine this condition by any of the other clinical methods.

### CONCLUSIONS

1. Pyelitis in pregnancy is dangerous in two respects: (a) Maternal mortality of 3.58 per cent, and fetal mortality of 15.8 per cent; (b) exacerbations occur unless adequately treated or unless urine becomes bacilli-free between pregnancies.

2. Catheterization of the atonic post-partum bladder often leads to serious sequelae.

3. There is no proved relationship between toxemia and pyelitis of pregnancy.

4. The length of time during which the urine remains infected in the puerperium varies tremendously both in adequately treated and in untreated patients so that no definite conclusions can be drawn. Each patient is therefore to be treated individually.

5. As a result of acute pyelitis the patient sustains permanent ureteral damage due to fibrosis with embarrassment of peristalsis and ureteral tone.

## A PROBLEM IN SEX CLASSIFICATION*

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MALFORMATIONS of the genital organs seldom impose any serious obstacle to the fundamental sex classification of the individual. In some cases abdominal operation is necessary to give definite information concerning the internal organs, but this usually clears the matter promptly. Even in the cases of mixed sex gland, that is, where one individual carries both ovarian tissue and testicular tissue, the sex determination is not difficult. All that is required is to preserve the gland tissue corresponding to the patient's preferences and instincts, and remove the other type. Occasionally, however, a case is encountered which is not covered by our usual methods of sex recognition and requires a much deeper consideration of what constitutes the real sex of an individual and how this primary sex may be modified or partly obscured by later pathologic developments. Such was the problem presented by the following recent case:

About the first of September, 1938, a young woman was sent to me for construction of a vagina. She was 28 years of age, and had never menstruated, though there had been some irregular bleeding when she was about 20 and again two years ago. On examination, I found the genital organs identical with those of a male pseudohermaphrodite. The conditions are shown diagrammatically in Fig. 1. There was the small hypospadiac penis, and back of that a vestibule with two openings, the one in front being the urethra, and the one a little farther back, an enlarged sinus pocularis. The testicles were in the groins.

The general build was masculine, with narrow hips compared to the shoulders. As shown in Fig. 2 there is marked hair growth, with masculine distribution. Also, the patient had a beard requiring regular shaving. Fig. 3 gives a general view of the external genitals. The patient had more breast tissue than is ordinarily found in the male.

Fig. 1.—Diagrammatic representation of conditions in male pseudohermaphroditism of the hypospadiac type. Anteroposterior section showing the small hypospadiac penis with the urethra opening at its base and the enlarged sinus pocularis opening into the perineal vestibule. (From Crossen and Crossen, *Diseases of Women*, The C. V. Mosby Company.)
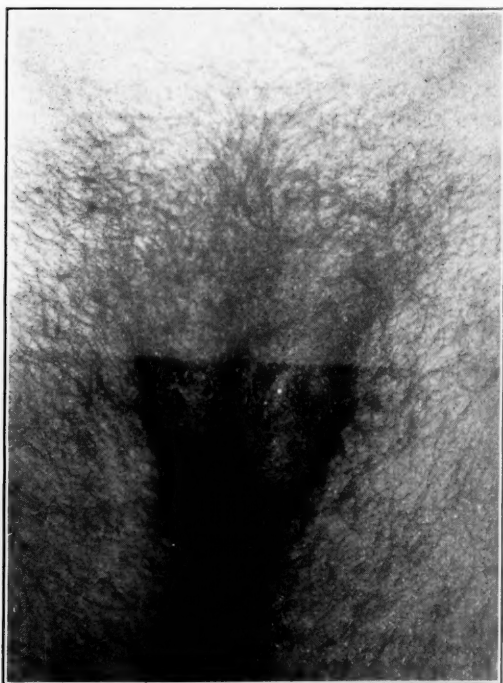


Fig. 2.—Showing the marked hair growth, with masculine distribution. The left testicle is coming down into the labium, while the right is higher in the groin.

When such conditions are present, the individual's inclinations and sexual desires ordinarily correspond with the male gonads, and in that case the classification as a male is correct. But in this case, the patient's instincts and preferences from childhood up, and the sexual desires and mental outlook of the present, were all strongly feminine.

This apparent sexual paradox made it necessary to determine if ovaries were present. Abdominal exploration was then carried out. This showed that there were no ovaries nor tubes nor uterus, the space between the bladder and rectum being entirely clear. With this operative revelation of no ovaries, the patient's earlier history became of special interest. During childhood there had been no departure from the ordinary activities of a girl. She went to the country school, got along very well with her studies, and associated with the other girls in their games. When not in school, she worked on the farm with the other children, doing her share of the heavy work. She always dressed and played as a girl. There were no tomboy inclinations, nor desire for boys' clothes nor amusements.
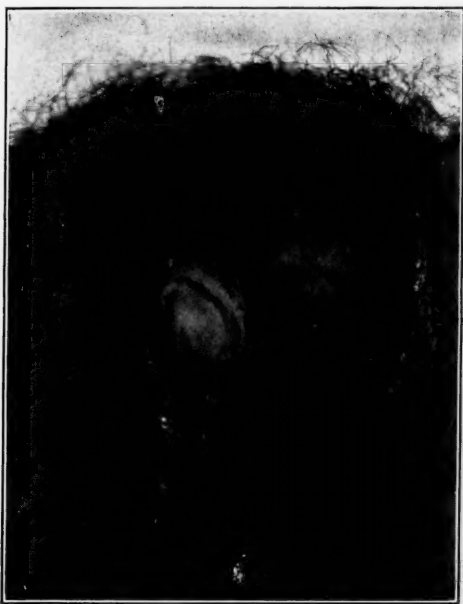


Fig. 3.—Showing the enlarged clitoris and the perineal slit leading to the vestibule, and also the enlargement of the left labium by the testicle in it.

Pubic hair appeared at about fifteen years of age, but there was no menstruation. Sex desire towards men was noticed at age of eighteen or twenty. At about twenty, she had a slight pinkish discharge for three or four days. This was repeated four or five times, at intervals she thinks of about a month.

There was no more bloody discharge until about two years ago, when sexual intercourse began. Immediately after the first coitus there was a very free bloody discharge, which stopped the next day. Two weeks later there was profuse flow for some days, and five weeks later another short flow, but not so free. The last two flows came spontaneously, without coitus. Since that time coitus has taken place frequently, without any bleeding or pain or other disturbance, except that the vagina is very short. Her sexual desires have always been toward men, never shifting to women.

Here, then, was a patient with strong feminine instincts, sexual desires, and general outlook on life, but with testicles and no ovary. What sex classification should be made of such an individual? That

was the important and difficult problem which had to be worked out
before anything could be done in the way of constructive surgery for
the patient, because the type of surgical help required depended on
whether the individual was to live as a man or as a woman.

If I followed the gonads and classified the patient as a male, I was
directly opposed by the whole record of the individual's instincts,
sexual desires and response, and the outlook into the future. If I fol-
lowed the latter and classified the patient as a female, there was no
ovarian tissue on which to rest the decision. A female with testicles
and no ovary seemed paradoxical, and of doubtful authenticity. Still
the patient had to be classified one way or the other. There was no
neutral ground.

What are the dependable criteria for determining the primary sex
of an individual? Of course, in this endocrine age, the gonads and
their hormones occupy the center of the stage and are looked upon
as the decisive factors in the sexual field. But are they? Such a case
as this casts serious doubt on their fundamental importance in deter-
mining the primary sex personality. The gonad with its hormones
may be an effect instead of a cause, as far as primary sex is concerned.
Their influences are easily seen and may seem all-important, but there
are other influences which enter into the building up of the instincts
and directing forces. There is the whole nervous and mental system,
which is as important a part of the individual as the gonads, and prob-
ably comes from just as strong genetic factors.

Wolf,[1] of the University of Bern, holds that in the chromosomal arrangement
and determination of primary sex an impress is made on the somatic cells which takes
precedence over that on the gonadal elements, which develop later. In discussing
such cases, he states that the somatic and psychic impress seems predominant and
that, though hormones play a role in later structural developments, the sex of the
somatic cells is decisive. Novak,[2] in discussing his case mentioned later, states
"such patients as I have described represent genetic females, in which gonadal re-
versal took place at a very early phase of development, with complete replacement
of ovarian by testicular elements."

Reviewing then the two sets of phenomena which help in primary
sex classification, we have in this case a personality with well-developed
female instincts, preferences, sexual desires, and mental outlook, and
on the other hand rudimentary male gonads and associated secondary
developments. The testicles undoubtedly lack spermatozoa formation,
and hence have stopped short of full development. The spermatic
cords and prostate are still more rudimentary, being hardly appre-
ciable in the abdominal exploration. The phallus is rudimentary, and
resembles an hypertrophied clitoris as much as a hypospadiac penis.
The canal in the perineum, which admits a finger for about an inch,
may as well be considered a small vagina as an enlarged sinus pocu-
laris. In such a case, of good development of instincts and mental
make-up and poor development of physical structures, it seemed to me
that the individual should be classed on the side of the well-developed
set of phenomena. Hence, I felt that the patient should be considered

as primarily and essentially a female, and that our advice and treatment should be directed accordingly.

Now, could any substantial support be found for thus classifying and treating as a female, a patient with testicles and no ovary? The decision was a serious matter, for on it rested the direction of the future life-activities of the individual. Also, the decision had to be made promptly, as the patient was recovering from the abdominal exploration and was about ready for the further surgical work required.

In the short time available, I found records of seven comparable cases, that is, of cases in which predominant female sex desires and preferences persisted in the presence of testicles without an ovary. Of course, there are many other reported cases of this type, but these seven cases had been handled in recent years, under the present fund of knowledge concerning endocrines and sex determination, and hence their handling was studied with particular interest.

In these seven cases, the absence of ovaries was confirmed by abdominal exploration in five, and seemed fairly certain in the other two. The testicles were removed in six cases, and in the other case they were shifted from the groin to inside the pelvis. The hypertrophied clitoris was removed in four cases. In all of the patients operation was followed by improved social and sexual adjustment and continuation of normal libido. The essential details of these reported cases applying to our problem, were briefly as follows:

CASE 1.—(Mishell.[3]) Patient, aged 35, was of feminine build, but had never menstruated. She came for treatment for tender lumps in the groins. Examination showed double inguinal hernia with a testicle in each. External genitals were normal, with vagina represented by a small canal three inches long ending bluntly with no cervix.

Abdominal exploration showed no ovaries, tubes or uterus. The testicles were removed, and the hernias repaired. Improved adjustment. Patient returned to her work. Normal libido.

CASE 2.—(Mishell.[3]) Sister of preceding patient, aged 23, feminine build, complained of tender lumps in groins. Abdominal exploration showed no ovaries, tubes, or uterus. Testicles were removed. Improved adjustment and patient continued with good health. Headache which had troubled her disappeared after the operation.

CASE 3.—(Mishell.[3]) Sister of the preceding, aged 32, had lumps in the groins and had never menstruated. Examination showed the same conditions in this sister as in the other two. Feminine build, good breasts, no hirsutism, and instincts and feelings all feminine. The only thing special was that she became gray in childhood at the age of nine. The patient was well-adjusted, emotionally stable, had no complaint, and no operation was required. This was one of the two cases in which the absence of ovaries was not confirmed by abdominal operation, but careful pelvic palpation along with the similarity to the other two sisters excluded ovaries with fair certainty.

Rubovitz:[4] Patient, aged 39, masculine build, beard, testicles in groins, hypertrophied clitoris, short vagina, came complaining of severe libido and painful erections. The testes and the hypertrophied clitoris were removed, and the short vagina lengthened. There was improved adjustment and normal libido. The relief from the annoying erections was probably due more to removal of the enlarged and hypersensitive clitoris than to removal of the testicles, for as pointed out later the removal of the testicles seems to exert no influence on the sexual desires and re-

sponses of these patients. This is the other case in which the absence of ovaries was not confirmed by abdominal operation. But by deep palpation and the use of pneumoperitoneum, it was felt that ovaries were excluded with fair certainty.

Wharton:[5] Patient, aged 18, was of masculine build from the waist up and feminine build from the waist down. Had a beard. There was double inguinal hernia, hypertrophied clitoris and short vagina. On this diagnosis, the troublesome hypertrophied clitoris was removed and the hernia operation begun. In the hernial sac a testicle was found. An incision on the other side showed another testicle. The incisions were then closed, and later it was explained to the patient that a serious mistake had been made in amputating the supposed enlarged clitoris, which was in fact a penis, and that she was not a female but a male with two testicles. But the patient took quite a different view of the situation. She stated that no mistake had been made in amputating the enlarged clitoris, that she knew she was a woman and that she intended to live as such, and insisted on removal of the testicles. The testicles were finally removed, and abdominal exploration showed no ovaries. Improved adjustment. Normal libido. The patient married and sexual intercourse was satisfactory on her part and also on the part of the husband, except that the vagina was short. It was lengthened later.

Young:[5] Patient, aged 21, masculine build, but no beard. Lumps in the groin, no vagina. Patient was engaged to marry. Abdominal exploration showed no ovaries, tubes, or uterus. A vagina was constructed and the inguinal testes were put back in the pelvis instead of being removed. Improved adjustment. Normal libido.

Novak:[2] Patient, aged 19, masculine build, beard, hypertrophied clitoris, short vagina. In this case pelvic palpation showed bodies in the position of the ovaries, and about that size. Abdominal operation showed these bodies to be testicles in the usual position of ovaries and with a rudimentary broad ligament, but no ovaries, tubes, or uterus. The abdominal testes and the hypertrophied clitoris were removed. Improved adjustment. Normal libido. The vagina is to be lengthened later.

Our Case (for comparison). Patient aged 28, masculine build, beard, testicles in the groins, short vagina. Came for construction of vagina. Abdominal exploration showed no ovaries, tubes, or uterus.

It was clear then that those who had already struggled with the problem of the cases of this type had reached the same conclusion I had, namely, that the patient should be treated as a female. Some had reached this conclusion in the primary study of their patient, and others had been forced to it by later developments which confirmed and emphasized the predominance of the female element in the personality.

Having classified the patient as a female, with the right to live as such, the next step was to plan treatment to help as much as possible in that direction. The patient's two complaints were: first, the hair on the face which required frequent shaving and, second, the smallness of the vagina. So the two problems were to lessen the facial hair, by lessening the masculinity, and to lengthen the vagina. To accomplish these things, a combination treatment was planned consisting of (a) removal of the testicles, (b) administration of estrin preparations, and (c) stretching treatments for the short vagina.

Accordingly, I removed the testicles, doing the work under local anesthesia and checking each one with frozen section examination before removal, to exclude herniated ovary or ovotestis from removal. Later, Dr. Hobbs, in charge of the Laboratory, made a careful microscopic study of the testicles and there was no indication of ovarian tissue anywhere. As usual with retained testicles, there was no sper-

matozoa formation.   At the preceding abdominal exploration, Dr. Sanford made a critical palpation of the kidney areas and could find no indication of adrenal tumor.

Systematic stretching treatments for the vagina are being employed. If sufficient lengthening cannot be secured in that way then operation is to be carried out.   Estrin administration is being pushed with the double purpose of lessening the facial hair, by diminishing the masculinity, and of aiding the vaginal stretching by softening the pelvic tissues.

Various details discussed must be omitted here for lack of space, but it may be stated that in this case and in the reported cases the absence of ovaries and the presence of testicles seemed to exert little or no influence on the strong female desires and responses.   Despite the hindering presence of testes and later the lack of sex glands altogether, the patient's feminine personality continued the even tenor of its way.

An important point in taking care of such a patient is to avoid terms or expressions which may disturb her psychologic balance by making her uncertain as to her sex.   All records and explanations and reports should be made to conform to the correct primary sex, as worked out by careful study of the case.   The patient is already disturbed by the malformation which she wishes corrected, but as a rule she has no thought that she may not be a woman, and it is strongly inadvisable to put her further adrift on the sea of uncertainty by branding her as a male according to the old superficial structural classification.

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UNIVERSITY CLUB BUILDING

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**Kuschtalow, N. J., and Terentjewa, N. D.:   The Influence of Chemical and Biological Factors on the Microscopic Picture of Milk and Colostrum,** Arch. f. Gynäk. **165**: 335, 1938.

The transition of colostrum into breast milk is produced by the direct effect of hormonal stimulation.   Such stimulation arises in the pituitary, causing a degeneration of the colostrum bodies which become confluent and produce the fat globules of breast milk.   Experimentally, this change from colostrum bodies to fat bodies is hastened in vitro by pituitrin, and in vivo it increases the fat contents of the milk.   The activation of the secretory glands of the breast also hastens this transition.   The authors were unable to produce any changes in the colostrum by the addition of any other hormones, ferments, sera, urine, or various chemical agents which were tested.   The urine of pregnant women, however, did produce a characteristic microscopic change in the appearance of the colostrum bodies.

RALPH A. REIS

# CANCER OF THE CERVIX COMPLICATING PREGNANCY

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THE purpose of this paper is to report a case of cancer of the cervix complicating pregnancy, and by a search of the literature to determine if possible how much danger there is to the baby from exposure to radium during intrauterine life.

This condition is rare, occurring about once in 1,500 pregnancies, and the reason for this rarity is evident because usually cancer is a disease of later life or at least of the late childbearing age, whereas pregnancy is more common in younger women.

There is a tendency in many papers to discuss whether cancer of the cervix is a complication of pregnancy or pregnancy a complication of cancer, that is whether cancer antedated the pregnancy or developed after conception. Many writers argue that the diseased cervix tends to militate against conception. In the majority of the cases collected, cancer was not diagnosed until the second half of pregnancy.

Another academic controversy which seems to interest many writers is whether the coexisting pregnancy inhibits or accelerates cancer growth. This was not a major point in the research, but it was given consideration. However, the information obtained from most reports is thought to be insufficient to throw any light upon the controversy.

It would seem that expert knowledge is not a requisite for making a diagnosis; rather that thoroughness in examination, speculum visualization at the first prenatal visit and particularly the history of bleeding at any time during pregnancy, are of prime importance. In 5 of the cases of gross abnormalities of the baby, the reports stated that x-ray or radium was used for bleeding or for fibroid tumor in the first or second months of gestation, pregnancy not having then been diagnosed. These reports were all before the time of the Aschheim-Zondek test but nevertheless were evidence of gross carelessness, and they were all published in x-ray, not obstetric, journals.

In a consideration of the treatment we are confronted with a perplexing problem. In general it would seem, as in most all surgical complications of pregnancy, a good policy to treat the complication regardless of the pregnancy. The more or less commonly accepted present-day treatment of cancer of the cervix in the nonpregnant woman is radium, but it is also more or less commonly believed that radium treatment of cancer of the cervix in pregnancy is attended with grave risk to the baby. Study of Tables II and III would seem to lead one to believe that this danger is exaggerated. Such would seem to be true where treatment is not instituted until the second half of gestation; of 14 cases reported in this category, only one resulted in an abnormal baby and in

that it is questionable whether radium was the cause of the abnormality. Some of the defects most likely were congenital and must have existed before the time of the treatment.

The problem then really revolves upon what to do with the condition when seen during the early months of pregnancy. Judging from this study this is indeed a rarity; in the whole series there are only 13 cases reported. In such a situation should one be fortunate enough to consider the cancer to be early, hysterectomy might be performed, with radium or x-ray preceding or following the operation.

TABLE I. MISCARRIAGES

| AUTHOR | AGE | PARA | GESTA-TION | DIAG-NOSIS | TREAT-MENT | RESULT |
|--------|-----|------|------------|------------|------------|--------|
| 1. Zimmerman | | | | | Radium | 3 patients miscarried shortly after radium given in middle of pregnancy |
| 2. McGlinn | 31 | | 3 months | Cancer of cervix | Radium | Miscarried four weeks later |
| 3. Tropea-Mandalari | 40 | | 3 months | Cancer of cervix | Radium | Miscarriage |
| 4. Brouha | | | | | | 7 patients treated in early months followed shortly afterward by miscarriage |
| 5. Mundell, J. J. | 29 | | 2 months | Cancer of cervix | Radium | Miscarriage |

TABLE II. PATIENTS WITH ABNORMAL BABIES

| AUTHOR | AGE | PARA | DIAG-NOSIS | GESTA-TION | TREAT-MENT | DELIVERY | RESULT |
|--------|-----|------|------------|------------|------------|----------|--------|
| 6. Aschenheim, E. | 37 | Mult. | Myoma | Early | X-ray | Normal confinement | Gross abnormalities, mentally deficient |
| 7. Stettner, E. | 41 | Mult. | Myoma and bleeding | 8 months | X-ray | Normal confinement | Gross abnormalities, mentally deficient |
| 8. Abels, H. | 34 | Mult. | Metrorrhagia | Full term | X-ray | Normal confinement | Microcephalus |
| 9. Schaab, A. | 40 | Prim. | Fibroma | Early | X-ray | Cesarean section | Microcephalus |
| 10. Ries, E. | 24 Mentally and physically defective | | Metrorrhagia | 4 months | X-ray | Spontaneous labor | Stillborn hydrocephalus. Absence right kidney. Latter antedated treatment |
| 11. Goldstein, L., and Murphy, D. P. | | | Cancer of cervix | 6 months | Radium | Normal spontaneous labor | Mentally defective |
| 12. Gal, F. | | | Cancer of cervix | | X-ray | Spontaneous labor | Microcephalus |
| 13. Petenyi, G. | | | Cancer of cervix | Fifth to seventh month | X-ray | Spontaneous labor | Microcephaly and eye damage |

TABLE III.  PATIENTS WITH NORMAL BABIES

| AUTHOR | AGE | PARA | DIAGNOSIS | GESTATION | TREAT-MENT | DELIVERY |
|---|---|---|---|---|---|---|
| 14. Neill, W., Jr. | 32 | Mult. | Cancer of cervix | 5 months | Radium | Cesarean section |
| 14. Neill, W., Jr. | 21 | Mult. | Cancer of cervix | 6 months | Radium | Cesarean section |
| 14. Neill, W., Jr. | 28 | Mult. col-ored | Cancer of cervix | 7½ months | Radium | Cesarean section and supravaginal hysterectomy |
| 15. Smith, F. R. | 36 | Mult. | Cancer of cervix | 6½ months | Radium | Cesarean section, 8 months |
| 16. Fagioli, M. | 28 | Mult. | Cancer of cervix | 6 months | Radium | Cesarean section |
| 17. Amico-Roxas, S. | 27 | Mult. | Cancer of cervix | 6 months | Radium | Cesarean section and hysterectomy |
| 18. Zimmerman | 33 | Mult. | Cancer of cervix | 5 months | Radium | Normal confinement |
| 19. Paroli, G. | 29 | Prim. | Cancer of cervix | 3 months | Radium | Normal confinement |
| 20. Van Rooy, A. W. | 41 | Mult. | Cancer of cervix | 4 months | Radium | Normal confinement |
| 21. Berkeley, C. | 34 | Prim. | Cancer of cervix | 6 months | Radium | Cesarean section |
| 22. Brouha, M., and Gosselin | 31 | Mult. | Cancer of cervix | 6 months | Radium and x-ray | Cesarean section |
| 23. Condamin, R. | 38 | Mult. | Cancer of cervix | 5 months | Radium | Spontaneous normal confinement |
| 24. Couvelaire | | | Cancer of cervix | 5 months | Radium | Cesarean section, 8½ months |
| 25. Povey | 34 | Mult. | Cancer of cervix | 3½ months | Radium | Spontaneous normal confinement |
| 26. Hoffman, H. | 27 | Mult. | Cancer of cervix | 5 months | Radium | Normal confinement |
| 27. Kane, H. F. | 41 | Prim. | Cervical polyp | 3 months | Radium | Cesarean section* |
| 28. Herold, K. | | | Cancer of cervix | 5 months | X-ray and radium | Spontaneous normal confinement |
| 29. Lacomme | 39 | Mult. | Fibroid | 4 months | Radium | Normal confinement |
| 29. Lacomme | 39 | Mult. | | 3 months | Radium | Normal confinement |
| 30. Titus, E. W. | | Mult. | Cancer of cervix | 5 months | Radium | Normal confinement |
| 31. Mundell, J. J. | 33 | Mult. | Cancer of cervix | 6 months | Radium | Classical cesarean section |

*Baby was stillborn but no gross abnormality.

More often however the cancer is likely to be too far advanced for such a choice and many writers have suggested radium treatment followed shortly afterward by emptying the uterus, fearful of letting the pregnancy continue because of the great damage to the baby. Objection is offered to this plan because it is conceivable that operative manipulation on such a diseased cervix at this stage of gestation would too greatly endanger the life of the mother from sepsis or

hemorrhage.   Should one wish to adopt such a course, probably the safest method would be by abdominal hysterotomy.

It would seem, in view of the study of the cases reported in this series, that one might have a third choice.   That would be, to give a smaller dose of radium, hopeful that it would, at least for the time being, retard the malignant growth and at the same time not be too hazardous to the baby; this to be followed by the customary radium dose after the pregnancy had advanced midway.

## CASE REPORT

Mrs. G. S., aged 33 years, para vi, had had all normal pregnancies and labors, youngest child aged 6 years, other history irrelevant and no family history of cancer. The patient was a well-developed, well-nourished woman, first seen in the dispensary at Georgetown Hospital May 27, 1938.   Last menstrual period Dec. 21, 1937.   Expected date of confinement Sept. 28, 1938.   Patient stated that she felt well during pregnancy until April 12, when, while moving heavy furniture, she believed she strained herself, as she experienced dull pain in the back and lower abdomen.   The pain continued upon any exertion.   On May 26 she fell in a sitting position and the next day passed two large blood clots, and on May 28 she came to the maternity clinic fearing that she would abort.   Examination revealed the fundus at the level of the umbilicus, fetal heart 130 in left lower quadrant, and speculum examination showed an ulcerated craterlike area on the posterior lip of the cervix.   She was admitted to the Hospital June 8 when a biopsy was performed and the pathologic report was as follows:

"Microscopically the section presents one large area of densely packed, markedly anaplastic stratified epithelial cells.   These cells are very irregular in size and shape and there are numerous mitotic figures, some in multipolar division.   The deeper underlying tissue has a dense infiltration of lymphocytes.

"*Diagnosis:*  Squamous cell carcinoma, Grade IV."

The treatment consisted of 50 mg. of radium applied to the cervix for thirty-six hours each application, on June 12, 22, and 27, a total of 5,400 mg. hours.

From the time of the treatment until a classical cesarean section was done on September 15, thirteen days before the expected date of the confinement, she complained frequently of dull aching pain in the lower abdomen relieved somewhat by mild sedatives.   At no time did the pain simulate labor pains.

On September 15 a classical cesarean section was performed, and the puerperium was uneventful.   The baby, a male, weighed 6 pounds 11 ounces and the pediatric service reported that so far as could be ascertained the baby was normal.   April 18, 1939:  The baby is developing as a healthy normal child.

## Analysis of the cases collected from the literature is as follows:

All but four women were multiparas.   There were 13 cases in which miscarriage followed the application of radium during the first three months of gestation and 3 cases where it followed radium treatment in the middle of pregnancy.

There were 8 patients treated with x-ray or radium with grossly abnormal babies. Of these there was one patient with cancer who was treated with radium at the sixth month.   Two patients with cancer were treated with x-ray, one at the fourth month and the other between the fifth and seventh months.   The other 5 were treated for myoma or for metrorrhagia, all with x-ray.   Two were in the early months, one at the fourth month, one at the eighth month, and one at term.   It is questionable that x-ray therapy at the eighth month and at term was the cause of fetal abnormalities.   The wisdom of treating these 5 cases of bleeding with x-ray is certainly questionable.   All 8 patients in this category had spontaneous deliveries.

In 21 patients treated with radium the babies were normal.   Nineteen of these cases were for cancer of the cervix, one for fibroid and the diagnosis was not given in one.

In 6 of this group, treatment was given during the first half of pregnancy, and in 15 during the fifth and sixth months.

In 11 of this group the labor was normal, in 8 cesarean section was performed and in only 2 was cesarean section followed by hysterectomy.

Of 42 cases collected, 21 patients or 50 per cent, had normal babies, 8, or 19.04 per cent, had abnormal babies, and in 13, or 30.96 per cent, miscarriage followed shortly after the treatment.

Nine of these children were reported to be normal at the following ages: 2 years, 2 years, 3 years, 3½ years, 4½ years, 5 years, 8 years, 14 years, 20 years.

The last, 20 years old, reported by Sir Comyn Berkeley, is a girl who at the age of 15 broke the Olympic high jump record.

## COMMENT

Radium to the cervix in the early months of pregnancy may be attended with risk to the baby, but in the second half of pregnancy, study of this series would lead one to the conclusion that the treatment is not as hazardous as heretofore believed.

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**Miller, Norman F., and Todd, Oliver E.:** Conization of the Cervix, Surg. Gynec. Obst. **67:** 265, 1938.

Electrosurgical conization of the cervix is many times faster, simpler and a bloodless substitute for the Sturmdorf operation. The amount of tissue removed can be controlled and conization equals in efficiency any means of cervical gland reaming now available. Ultimate healing is but little slower than in the Sturmdorf procedure and the incidence of severe stricture probably not greater. In general, its use should be limited to women past the childbearing age and even in this group should not be looked upon as a substitute for the less radical office procedures now in use in the treatment of simple cervical disease. Conization is a desirable, quick, and convenient method of treating the cervix prior to subtotal hysterectomy.

WILLIAM C. HENSKE.

# A REVIEW OF THE RECORDS OF SYPHILITIC PREGNANT WOMEN TREATED AT THE LOS ANGELES MATERNITY SERVICE OVER A TEN-YEAR PERIOD

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O F THE numerous studies that have been recently made of syphilis in pregnancy, the most exhaustive and detailed have been those of the Cooperative Clinical Group.[1] The very abundant clinical material at the disposal of this group for study makes their reports and opinions authoritative.

In the various clinics designated to the treatment of syphilis in pregnant women there are many factors peculiar to the individual clinic which must be considered in determining the type of treatment that is apparently best suited to the individual clinic.

The following study was undertaken with the intention of presenting the problems peculiar to the treatment of syphilis in pregnant women who presented themselves at the Los Angeles Maternity Service over the period of the past ten years, with an attempt to evaluate the form of treatment given them.

### MATERIAL STUDIED

The total number of patients who were cared for at the Los Angeles Maternity Service over this period of time was 35,594. Of this number of pregnant women 969 were found to have syphilis. This incidence of 2.04 per cent is quite low in comparison to studies made in other similar clinics. Race seems to be an important factor in determining the incidence of syphilis in clinical patients. In this clinic approximately 50 per cent are Caucasian women, approximately 35 per cent are Mexican women, and the remaining 15 per cent are negroes.

### CLINICAL EVIDENCE OF SYPHILIS OR SUSPICIOUS HISTORY

Table I demonstrates that of the entire group of 969 syphilitic pregnant women there were 3 patients, or 0.31 per cent, who had primary lesions but no secondaries when they first presented themselves at the clinic. There were 13 patients or 1.34 per cent who had secondary eruptions but in whom no primary lesion was found. There were 10 patients or 1.03 per cent who had primary and secondary syphilis at their first visit to the clinic. Two patients, or 0.20 per cent, presented tertiary lesions. There was clinical evidence of congenital syphilis in 15 patients, or 1.54 per cent. Thus there were 43 pregnant women, or 4.44 per cent, of the entire 969, who had clinical evidence of syphilis at the time of their first visit to the clinic.

In taking the history of each patient at her first visit it was found that 44 women, or 4.54 per cent, gave histories of a lesion possibly primary and no history of a generalized eruption that might be interpreted as secondaries. There were 38 patients, or 3.92 per cent, who gave a history of eruption possibly secondaries, but no history of lesions that might have been considered primary. There were 19 women, or 1.96 per cent, who gave histories of lesions possibly primary and eruptions possibly secondaries. There were 336 women, or 34.67 per cent, who gave histories of abortion or stillbirth, and there were 74 patients, or 7.63 per cent, who gave histories of infant death. Thus there were 511 women, or 52.73 per cent, who gave histories suspicious of syphilitic infection.

TABLE I.   CLINICAL EVIDENCE OF SYPHILIS OR SUSPICIOUS HISTORY

| CLINICAL EVIDENCE OF SYPHILIS AT FIRST VISIT | | | SUSPICIOUS HISTORY | | |
|---|---|---|---|---|---|
| | NUM-BER | PERCENT-AGE OF 969 | | NUM-BER | PERCENT-AGE OF 969 |
| Primary but no secondaries | 5 | 0.31 | History of lesion possibly primary No history of generalized eruption | 44 | 4.54 |
| Secondaries but no primary | 13 | 1.34 | No history of primary but rash possibly secondaries | 38 | 3.92 |
| Primary and secondaries | 10 | 1.03 | History of lesion possibly primary and history of skin eruptions possibly secondaries | 19 | 1.96 |
| Tertiary lesions | 2 | 0.20 | History of abortion or stillbirth | 336 | 34.67 |
| Evidence of congenital syphilis | 15 | 1.54 | History of infant deaths | 74 | 7.63 |
| Total | 43 | 4.44 | Total | 511 | 52.73 |

There was one patient who presented herself at the clinic in the fifth month of pregnancy, whose blood Wassermann was negative and who presented no clinical evidence of syphilis nor did her history in any way suggest a possibility of syphilitic infection.  This woman was delivered at term of a syphilitic baby whose Wassermann was strongly positive.  The mother's Wassermann at delivery was also strongly positive.  This patient was apparently infected during pregnancy and although she was examined at bi-monthly intervals at the clinic throughout her remaining pregnancy, no primary nor secondaries were observed either by the patient or the physician.  This case supports the opinion that pregnancy may suppress primary and secondary manifestations of syphilitic infection.

## QUESTIONABLE SYPHILIS

There is a variance of opinion as to whether or not pregnancy may produce a positive blood Wassermann reaction in women who are not syphilitic.  Many clinicians with vast experience believe the blood Wassermann in pregnancy to be just as dependable as it is in the nonpregnant patient.

There was a relatively small number of women who presented themselves at the clinic who gave no history of syphilitic infection, no clinical evidence of syphilis, and who at their first visit had a weakly positive blood Wassermann.  These patients were requested to bring their husbands and any former children to the clinic for examination and blood study.  In those cases in which the husband and children gave no clinical nor serologic evidence of syphilis, the pregnant woman was not treated but returned for blood Wassermann examination each week for four weeks and then every second or third week for the remaining term of pregnancy.  There were 65 of these patients set aside for study.  The blood Wassermanns of these patients were observed to fluctuate from weakly positive to negative.  The majority would have one weakly positive Wassermann followed by several negative reactions and then another weakly positive test.  Many of them would have only one positive Wassermann and the remaining blood studies would be negative.  The patients in this group were instructed to return with their babies six weeks after delivery for examination.  Table II shows that 21 of these patients failed to return after delivery so were deducted from the study.  Of the 44 who did return, 41 mothers and their babies had negative blood Wassermann reactions, which remained negative as long as it was possible to follow them.  Nor was there any clinical evidence of congenital syphilis in the infants.  Of the remaining 3 cases in this group, one mother and her infant both had strongly positive Wassermann reactions and were both placed upon treatment.  Another of these women had a weakly positive blood Wassermann

TABLE II.   APPARENTLY NONSPECIFIC POSITIVE WASSERMANN REACTIONS IN PREGNANCY

| | NUMBER | PER CENT |
|---|---|---|
| Total patients studied | 969 | |
| Total patients in this group | 65 | 6.71 |
| Patients who failed to return for examination after delivery | 21 | 2.17 |
| Patients apparently syphilitic | 3 | 0.31 |
| Patients negative after delivery whose infants were also serologically and clinically negative for evidence of congenital syphilis | 41 | 4.23 |

six weeks after delivery.  Her infant had a negative blood Wassermann six weeks after delivery and presented no clinical evidence of congenital syphilis.  This mother and baby failed to again return to the clinic.  The third mother had a weakly positive blood Wassermann six weeks after delivery.  Her infant presented no clinical evidence of congenital syphilis, the Wassermann reaction was negative six weeks after delivery and remained negative for the two years that he remained under observation.  This mother took two years of treatment.  Her blood Wassermann reaction continued to vary from negative to weakly positive during the two years that she was treated.  It is possible that the behavior of this patient's Wassermann reaction was due to other causes than syphilis.  Thus it was found in a study of 44 patients in this series whom it was possible to follow after delivery, that 41 apparently did not have syphilis.  The incidence of apparently nonspecific positive blood Wassermann reactions in this group of pregnant women was therefore found to be 4.23 per cent.

### TREATMENT

The great majority of patients who attend the Los Angeles Maternity Service do not present themselves until the fifth month of pregnancy or later.  The problem therefore is to give these women as much treatment in the remaining weeks of pregnancy as the patient might be expected to tolerate, in an effort to secure a living nonsyphilitic infant.  For this reason a combined scheme of therapy has been adopted.

As soon as the diagnosis of syphilis is established a course of treatment is outlined for each patient.  Neoarsphenamine and a heavy metal* are given in combination.  The patient makes two visits to the clinic each week.  The neoarsphenamine is given on Wednesday and the heavy metal on Friday.  The patient is given a series of 6 to 8 weekly injections of neoarsphenamine (increasing from 0.15 to 0.45 gm.).  For the past three or four years the policy has been to continue the heavy metal without interruption throughout the remaining weeks of pregnancy.  After 6 to 8 injections of neoarsphenamine the patient remains on heavy metal alone for four weeks.  A blood Wassermann is then taken and another course of neoarsphenamine is given.  Following the suggestion of the Cooperative Clinical Group an attempt is made to arrange the courses of treatment in such manner that the patient receives intravenous arsenical treatments for several weeks prior to delivery.  The urine is examined twice monthly and the percentage of patients who have not tolerated this scheme of therapy has been found to be so small as to be practically negligible.

Of the 969 syphilitic women treated during pregnancy at the clinic for the ten-year period, 453 failed to return to the clinic with their babies after delivery for physical examination and blood study and so were deleted from this summary.  From the records of the 516 who did return with their babies for physical examination and blood Wassermann examinations, the following study was made.

For the purpose of comparison of treatment results the entire group has been arbitrarily subdivided into minimal, moderate, and maximal treatment.  In Table III,

*When this department was established ten years ago mercury was used in combination with neoarsphenamine.  For several years past, bismuth has practically supplanted mercury in the scheme of treatment.

TABLE III. A COMPARISON OF OUTCOME OF PREGNANCY AMONG SYPHILITIC WOMEN TREATED AND UNTREATED DURING PREGNANCY

| | NO TREATMENT | | MINIMAL TREATMENT LESS THAN 6 NEOARSPHENAMINE AND LESS THAN 10 HEAVY METAL | | MODERATE TREATMENT FROM 6 TO 10 NEOARSPHENAMINE AND 10 OR MORE HEAVY METAL | | MAXIMAL TREATMENT MORE THAN 10 NEOARSPHENAMINE AND MORE THAN 10 HEAVY METAL | |
|---|---|---|---|---|---|---|---|---|
| | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT | NUMBER | PER CENT |
| Total patients | 16 | | 264 | | 149 | | 84 | |
| Disastrous termination of pregnancy (abortion or stillbirth) | 2 | 12.5 | 20 | 7.5 | 9 | 6.04 | 0 | 0 |
| Living syphilitic infants | 11 | 68.75 | 53 | 20.07 | 21 | 14.1 | 6 | 7.14 |
| Satisfactory termination (living nonsyphilitic infants) | 3 | 18.75 | 191 | 72.35 | 119 | 79.86 | 78 | 92.86 |

minimal treatment refers to less than 6 intravenous treatments of neoarsphenamine and less than 10 intramuscular injections of heavy metal. Moderate treatment designates patients who received from 6 to 10 intravenous treatments of neoarsphenamine and 10 or more intramuscular injections of heavy metal. Maximal treatment refers to patients who received more than 10 treatments of neoarsphenamine and more than 10 injections of heavy metal.

## NO TREATMENT

There were 16 pregnant syphilitic women who failed to return for treatment before delivery. Of these patients 2, or 12.5 per cent, delivered stillborn infants. Eleven of these women, or 68.75 per cent, gave birth to syphilitic infants and 3 of these pregnancies, or 18.75 per cent, had a satisfactory termination: living, apparently nonsyphilitic infants.

## MINIMAL TREATMENT

There were 264 patients who received less than 6 intravenous injections and less than 10 intramuscular injections of heavy metal. Of this group 20 pregnancies, or 7.57 per cent, terminated in abortion or stillbirth, 53, or 20.07 per cent, resulted in syphilitic infants, and 191, or 72.35 per cent, produced living, apparently nonsyphilitic infants.

## MODERATE TREATMENT

There were 149 women who received from 6 to 10 intravenous treatments of neoarsphenamine and 10 or more intramuscular injections of heavy metal. Nine of these pregnancies, or 6.04 per cent, terminated in stillbirth or abortion, 21, or 14.1 per cent, resulted in living syphilitic infants, and 119, or 79.86 per cent, produced living, apparently nonsyphilitic infants.

## MAXIMAL TREATMENT

There were 84 patients who received more than 10 intravenous treatments of neoarsphenamine and more than 10 intramuscular injections of heavy metal. None of these pregnancies terminated in abortion or stillbirth. Six of these patients, or 7.14 per cent, gave birth to living syphilitic infants, and 78, or 92.86 per cent, produced living, apparently nonsyphilitic infants.

## THE SIGNIFICANCE OF A POSITIVE BLOOD WASSERMANN IN SYPHILITIC PREGNANT WOMEN

Table IV shows that of the 516 syphilitic pregnant women in this study 188 had negative blood Wassermann reactions.  Of these 188 patients, 181, or 96.28 per cent, bore living, apparently nonsyphilitic infants.  Two, or 1.06 per cent, of these pregnancies resulted in the birth of living syphilitic infants, and 5, or 2.66 per cent, terminated in abortion or stillbirth.

TABLE IV.  THE SIGNIFICANCE OF A POSITIVE BLOOD WASSERMANN IN SYPHILITIC PREGNANT WOMEN

| | PREGNANT WOMEN WITH NEGATIVE WASSERMANNS | | PREGNANT WOMEN WITH POSITIVE WASSERMANNS | |
|---|---|---|---|---|
| Total patients in group | 188 | | 328 | |
| | NUMBER | PER CENT | NUMBER | PER CENT |
| Disastrous terminations of pregnancy (Abortions and stillbirth) | 5 | 2.66 | 27 | 8.23 |
| Living syphilitic infants | 2 | 1.05 | 89 | 27.13 |
| Living nonsyphilitic infants | 181 | 92.28 | 212 | 64.64 |

There were 328 of this group of 516 patients who had positive blood Wassermann reactions; of these 328 pregnancies, 212, or 64.64 per cent, terminated in the birth of living nonsyphilitic infants.  Eighty-nine, or 27.13 per cent, resulted in the birth of living syphilitic infants, and 27, or 8.23 per cent, ended in abortion or stillbirth.

### SUMMARY

1. The incidence of syphilis in pregnant women who attended the Los Angeles Maternity Service of the period over the past ten years was found to be 2.04 per cent.

2. There were 4.44 per cent of the pregnant women in this study who presented clinical evidence of syphilis at their first visit to the clinic; 52.73 per cent gave histories suspicious of syphilitic infection.

3. Though the blood Wassermann is the chief reliance in the diagnosis of syphilis in pregnancy and frequently the only evidence of syphilitic infection, there were 41 patients, or 4.23 per cent, in this study in whom there was apparently a nonspecific positive blood Wassermann reaction at some time during pregnancy.

4. The chances of a satisfactory termination of pregnancy in a syphilitic woman are increased with the amount of treatment she is given in pregnancy.

5. A negative blood Wassermann is of great value in determining the probable outcome of pregnancy in a syphilitic woman treated in pregnancy.

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1052 WEST SIXTH STREET

# THE TREATMENT OF GONOCOCCAL VAGINITIS BY ESTROGENIC HORMONE

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THE original basis for the use of estrogenic hormone in the treatment of gonococcal vaginitis was the demonstration of the influence of the follicular ovarian hormone upon the vaginal mucosa.

Stockard and Papanicolaou[1] describe cyclic changes in immature rodents; Allen[2] in immature monkeys; and Mazer and Ziserman[3] in spayed rodents under stimulation of estrogenic hormones.

The description by Davis and Hartman[4] of the details of the changes in the vaginal mucosa in monkeys during the physiologic cyclic change is of considerable importance in understanding the results produced in gonococcal vaginitis by the use of estrogenic hormones. They demonstrated that during the cyclic change in the mucosa, the epithelium, under the influence of the follicular hormone, consists of the greatest number of epithelial layers in the midinterval of the menstrual cycle. The mucosa at that time is composed of an active basal layer, an inactive functional layer and, between the two, an intraepithelial zone of cornification which is known as Dierks' layer. Following ovulation, desquamation begins and proceeds by a crumbling away of the functional or the superficial layer. The basal layer is not, at any time, desquamated and in the adult, regeneration takes place as a result of proliferation of the cells in this layer.

It has further been demonstrated[5] that the vaginal acidity in the newborn female is high and that shortly thereafter, the acidity declines. This is thought to be due to the influence of the ovarian hormone carried over to the child from the mother, which influence is lost shortly after birth. A similar increase in vaginal acidity has been shown to take place under the influence of the follicular hormone when introduced into the immature monkey.[6] Lewis,[7, 8] utilizing these physiologic changes, was the first to employ the hormone in the treatment of children having gonococcal vaginitis. His results were reported as favorable. Brown,[9] TeLinde and Brawner, Jr.,[10] Huberman and Israeloff,[11] Miller,[12] Abrams,[13] Limper and Hieronymus,[14] Lewis and Adler,[15] Benson and Steer[16] have all reported successful results without subsequent changes in physiology or damage to any structure in the patients as a result of the hormone employed.

Phillips,[17] Nabarro and Signy,[18] Wrana,[19] and Witherspoon[20] did not have similar success and warned against the possible dangers in the use of estrogenic hormone.

In order to determine from our own experience the value of the estrogenic hormone in the treatment of gonococcal vaginitis, a study was undertaken in three of the Social Hygiene Clinics of the Department of Health. In all, 108 patients were treated and observed for a sufficient length of time to report results. Their ages varied from three weeks to fourteen years. The diagnosis, in every instance, was based upon the presence of purulent vaginal discharge and gram-negative intracellular diplococci in the smear. No cultural diagnosis was employed.

## METHOD OF TREATMENT

Amniotin* in capsules containing 1,000 international units was the medication employed. The mother was instructed in the clinic, by actual demonstration, in the method of using the capsules. After gently cleansing the external genitalia, the labia were separated and one capsule was introduced through the hymen into the vagina, just before bedtime. One capsule was introduced each night. No other treatment and no douches were employed.

## CRITERIA OF CURE

The patients continued under treatment until all clinical evidence of the disease disappeared. Smears at weekly intervals were taken in all cases. The determination of cure, however, was not begun until the clinical symptoms had disappeared. At this point, treatment was discontinued and numerous successive smears were taken for a period of two months. The minimum number of smears taken was six from each patient. If these smears were negative, subsequent observation, clinically and bacteriologically, was continued for six months thereafter. At the end of this time, the patient was discharged as cured, if all examinations were negative.

## RESULTS OF TREATMENT

Of the 108 patients treated, 92 appeared to be cured after a period of treatment varying from 14 to 435 days, the weighted average being 149.8 days. However, 24 of these patients relapsed in an average of 109 days, after being apparently cured. Sixteen patients were never cured. This makes it appear that 68 patients were permanently cured, so far as our observation of these cases went. The details of results in the various clinics appear in Tables I and II.

### TABLE I. CLINICAL FINDINGS

| CLINIC | NO. OF PA- TIENTS | NO. OF CURES | DURATION OF CURE (IN DAYS) | | | NO. OF RE- LAPSES | TIME OF RELAPSE (IN DAYS) | | | NO. OF CASES PERMA- NENTLY CURED |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | EARLY | LATE | AVER. | | EARLY | LATE | AVER. | |
| St. V. | 20 | 16 | 53 | 95 | 75 | 3 | 41 | 56 | 49 | 13 |
| C. H. | 43 | 34 | 14 | 270 | 113 | 9 | 7 | 70 | 31 | 25 |
| C. | 45 | 42 | 35 | 435 | 208 | 12 | 45 | 270 | 183 | 30 |
| Total | 108 | 92 | | | 149.8 | 24 | | | 109.3 | 68 |

### TABLE II. LABORATORY FINDINGS

| CLINIC | NO. WITH NEG. SMEAR | TIME FOR NEG. SMEAR (IN DAYS) | | | NO. OF RE- LAPSES TO POS- ITIVE | TIME OF RELAPSE TO POS. (IN DAYS) | | | REMAIN- ING POSI- TIVE | POSI- TIVE REC- TALS |
|---|---|---|---|---|---|---|---|---|---|---|
| | | EARLY | LATE | AVER. | | EARLY | LATE | AVER. | | |
| St. V. | 13 | 30 | 64 | 48 | 3 | 7 | 485 | 51 | 4 | 4 |
| C. H. | 25 | 7 | 210 | 36 | 9 | 14 | 63 | 42 | 9 | 0 |
| C. | 30 | 5 | 120 | 23 | 12 | 8 | 252 | 72 | 3 | 9 |
| Total | 68 | | | 32.8 | 24 | | | 56.5 | 16 | 13 |

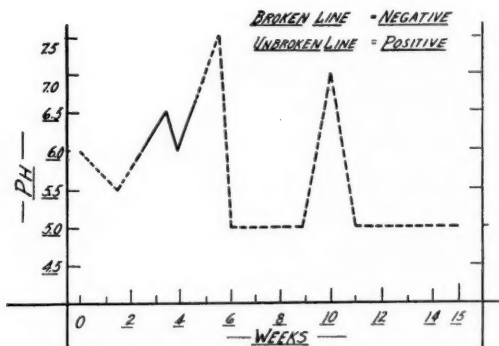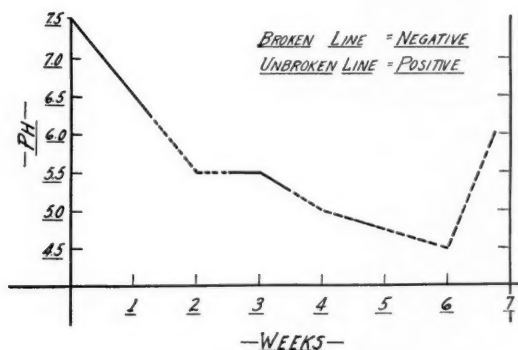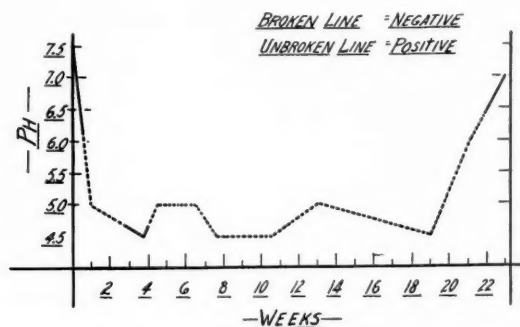## THE INFLUENCE OF VAGINAL ACIDITY ON SMEARS

The acidity of the vaginal secretions was determined in our patients in relation to the presence of gonococci in the smear; 993 such observations were made. "Nitra-

*The amniotin was supplied by E. R. Squibb & Sons.

zine paper''* was used for pH determinations and proved to be quite satisfactory.

The combined results of smear examinations and the concomitant vaginal acidity readings are shown in Table III.

The smear reports in relation to vaginal acidity showed no consistent relationship as can be seen from Graphs 1 to 6.
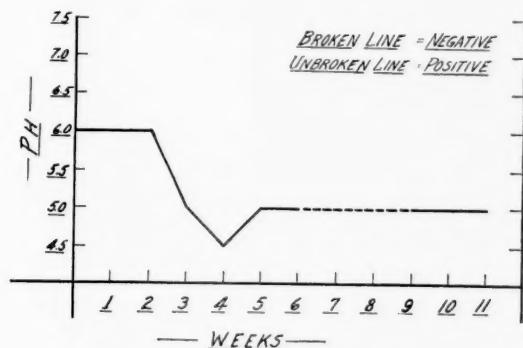
Graph 1.—Vaginal pH smear relationship.

Graph 2.—Vaginal pH smear relationship.

Graph 3.—Vaginal pH smear relationship.

*Nitrazine paper was supplied by E. R. Squibb & Sons.

TABLE III.  COMBINED REPORT OF CLINICS WITH 108 PATIENTS, FROM WHOM 993
SMEARS WERE TAKEN

| SMEAR | TOTAL NUMBER | pH VALUES | |
| --- | --- | --- | --- |
| | | 7.5-6.5 | 6.0-4.5 |
| Positive | 223 | 104 | 119 |
| Negative | 765 | 133 | 632 |
| Doubtful | 5 | 4 | 1 |
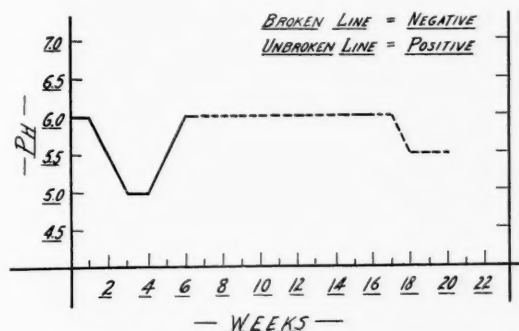


Graph 4.—Vaginal pH smear relationship.



Graph 5.—Vaginal pH smear relationship.
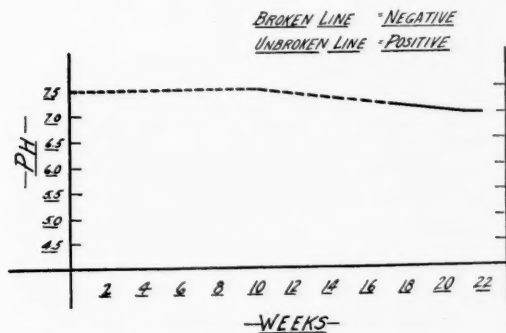


Graph 6.—Vaginal pH smear relationship.

## DISCUSSION

The favorable results, reported by various observers, produced by the use of the follicular hormone in gonococcal vaginitis have been attributed to the production of a mature type of vaginal mucosa following the administration of the ovarian hormone. This increase in the layers of vaginal epithelium is said to protect the tissues from penetration of gonococci and allow of the destruction by phagocytosis of the gonococci which have already penetrated into the submucosa. This explanation fails to take into consideration the fact that in every so-called gonococcal vulvovaginitis, the cervix is involved and that the cervical infection may, and often does, invade the parametrial lymphatic vessels.

While it is true that the cyclic change in the vagina occurs and that as a result of such cyclic change the discharge is diminished, no cyclic change has been irrefutably demonstrated in the cervical mucosa. This would tend to explain the number of patients who failed entirely to respond to hormone therapy.

The large percentage of relapses would indicate that phagocytic destruction of the gonococci in the submucosa does not occur in a large number of patients.

In addition, our experience in the adult female indicates that women may harbor the gonococci in the tissues for long periods of time without apparent evidence clinically or bacteriologically and nevertheless may act as sources of infection. It would, therefore, seem that the cyclic change in the vaginal mucosa cannot be advanced as the explanation of apparent cures.

The effect of the acidity on the life and growth of the gonococcus is too uncertain as demonstrated by the positive smears obtained in our series at pH levels of from 4.5 to 7.5. In addition, gonococci may be grown on culture media of a wide variety of acidity varying from 6.2 to 8.0.[21]

It would, therefore, seem that the explanation of apparently favorable results as being due to the increase of vaginal acidity resulting from the use of ovarian hormone which acidity inhibits and destroys the gonococci present is also doubtful.

The possibility remains that the disease in those who seem to be apparently cured may only be dormant and may relapse at some subsequent time. Such a possibility indicates the need for more thorough and exacting methods for determining cure in these patients.

The time required for apparent cure in our series is approximately the same as in our patients previously treated by other modalities.[22]

## SUMMARY AND CONCLUSIONS

1. One hundred eight patients were treated with amniotin in capsules containing 1000 international units inserted into the vagina every night.

2. Ninety-two patients, or 85 per cent, were apparently cured. The average time required for cure was 150 days.

3. Twenty-four patients, or 22 per cent, relapsed. The average relapse occurred in 109 days.

4. Sixty-eight patients, or 63 per cent, were seemingly permanently cured.

5. Sixteen patients, or 15 per cent, were unaffected and had persistently positive smears throughout the treatment.

6. The vaginal acidity showed great variations in relation to positive smears.

From the above, it would appear that although the treatment with amniotin capsules is simple and produces no apparent permanent physiologic damage, the results so far obtained are not conclusive. The uncertainty of the ultimate results with this treatment indicate the necessity for prolonged follow-up in those apparently cured.

The desirability of more intensive efforts to determine when cure is established is obvious, and investigation for this purpose along with other phases pertaining to this disease is urgently needed.

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**Strassman, Erwin O.: The Theca Interna Cone and Its Role in Ovulation,** Surg. Gynec. Obst. **67:** 299, 1938.

Ovulation is a mechanical process stimulated by the endocrine glands. Based on more than 18,000 serial sections of ovaries from human beings and mammals, the following facts were ascertained:

Universally an eccentric growth of the theca interna of the growing follicle was found. This one-sided proliferation of the theca interna is always directed toward the surface of the ovary. It forms a cone which is wedge shaped on the cut surface, infiltrates and penetrates the surrounding tissues, thus making a path for the growing follicle.

The growing Graafian follicle ascends to the surface of the ovary by following the line of least resistance which is provided by the cone of the theca interna. A more or less marked degree of edema is present in the surrounding tissues, which facilitates the mechanical progress of the ascending follicle.

WILLIAM C. HENSKE.

# PREGNANCY ASSOCIATED WITH CHRONIC
# ULCERATIVE COLITIS

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MANY factors predisposing to infection of the colon by the organism of chronic ulcerative colitis (thromboulcerative colitis) have been encountered. These have been discussed in previous publications.[1,2] Occasionally the infection has arisen in the course of an apparently normal pregnancy. Because of this, physicians have usually expressed great concern about pregnancy in the presence of chronic ulcerative colitis. As time went on, it was noted that some women, who became pregnant while active symptoms of the disease were at hand, experienced complete relief of symptoms of their colitis during the progress of their pregnancy. Frequently physicians dealing with such a combination of circumstances had thought it wise to end the pregnancy. Because of such experiences and the great anxiety generally apparent when the two conditions coexist, we felt that it would be of some interest to review the records of a series of patients who had become pregnant in the course of an active ulcerative colitis; or who had had ulcerative colitis, whose symptoms had become quiescent and who then had become pregnant. This is not a report of all of the patients who have come under our care or who have brought to our attention this combination of circumstances. It does, however, represent a series of patients who have been followed fairly closely.

Many women who have recovered from this most intractable illness have asked about the advisability of pregnancy. This question has frequently been asked months and years after recovery. It is well recognized that chronic ulcerative colitis is a disease of youth, and so when patients who have had the disease have become symptom-free and are married later, they have naturally experienced a concern about future childbearing. No one's experience with this combination of circumstances has been great enough to answer this question correctly. It was felt that a study of this series of cases might help us to answer the question more satisfactorily than before.

This series consists of only 17 women between the ages of 21 and 34 years. The 17 patients had 18 deliveries and 4 miscarriages (Table I). One of the patients is now pregnant and the symptoms have remained under control during the progress of her pregnancy, although the disease is not entirely quiescent. After 9 of the deliveries, the symptoms of colitis were improved (53 per cent). After 5 deliveries (29 per cent) the symptoms became worse. After 2 deliveries the symptoms of colitis

were unchanged.   After 1 delivery so little change was noticed that
the patient was unwilling to express herself.   In one instance, the
symptoms of colitis began after delivery.   Again after 2 (50 per cent)
of the miscarriages, the symptoms of the colitis were definitely im-
proved.   After a third miscarriage the symptoms seemed somewhat im-
proved and after a fourth miscarriage the symptoms were unchanged.
An illustrative case history follows:

CASE 1.—A single woman, aged 25 years, from Ohio came under the care of
the Mayo Clinic in November, 1934, with a history of bloody dysentery of two
months' duration.   At that time the proctoscopic picture was typical of that seen
in the streptococcal type of chronic ulcerative colitis.   The lesions were found to
be limited to the rectum and sigmoid portions of the large intestine.   The patient's
general condition was otherwise satisfactory.

TABLE I.   EFFECT OF PREGNANCY ON COLITIS IN 17 INDIVIDUALS WHO HAD 18
DELIVERIES AND 4 MISCARRIAGES

|  | COLITIS | | | |
|---|---|---|---|---|
|  | IMPROVED | WORSE | STARTED | UNCHANGED |
| After delivery | 9 | 5 | 1 | 3 |
| After miscarriages | 3 | | | 1 |

In spite of usual treatment, including the administration of vaccine, the patient's
condition failed to improve but remained the same until her return in January,
1935.   At that time a course of the anticolitis serum was given and soon progress
was quite satisfactory.   She became symptom-free and had been so for about a
year when she was married.   In January, 1937, pregnancy was noted.   The bowel
condition remained unchanged until the middle of May, 1937, when there began
cramping and abdominal pains with the passage of five to six bloody rectal dis-
charges daily.   When the patient failed to improve on symptomatic measures, she
was advised to have her pregnancy terminated.   The condition of her bowels be-
came slightly worse and she returned to the clinic in the seventh month of her
pregnancy.   She was hospitalized; treatment with serum was recommended.   The
usual program was outlined and the bowels gradually improved.   By the time of an
uneventful delivery at full term, the symptoms of colitis had entirely subsided.
This was in October, 1937.   The patient has had no further symptoms of her colitis
up to this date.

COMMENT

Judging from a very large number of inquiries received about the risk
of colitis complicating pregnancy, it is evident that there is no uniform
opinion about the management and prognosis of these coexisting condi-
tions.   Many have thought that the association of pregnancy and chronic
ulcerative colitis should be viewed much as tuberculosis and pregnancy
are considered.

This series of patients presents an interesting problem.   It cannot be
said that the patients in whom good effects followed pregnancy were
simply those in whom the colitis was milder.   In all of them it was
moderately severe, and several of the patients who recovered and who
have never had a recurrence of the disease suffered from the fulminating
septic type of ulcerative colitis.   One of these women has had no sign
or symptom of her former colitis for twelve years.

Again, it was in some of the less severe cases that no effect on the

colitis occurred. It is possible that we are dealing with a somewhat different form of the colitis in these cases. It seems more likely, however, that some product of metabolism is present in these cases in variable amounts. Perhaps there is a foreign protein reaction to such a substance, simulating the response to an allergen. After all, the cause or causes of the toxemias of pregnancy are by no means clear. Some have thought that rapid proteolysis in the chorionic villi of the pregnant woman leads to the formation of an antiferment; others have thought that there is a dislocation of the normal values in the blood of estrin, prolan, and progesterone; still others have considered an unusual absorption of the split products of digestion from the intestinal tract; and others have thought of the early toxemia of pregnancy as a neurosis.

There seems little doubt that the protein requirement of the average patient suffering from chronic ulcerative colitis is not met, owing to interference with absorption as well as to failure of adequate intake.[3] These patients require increased intake of protein. The same can be said of pregnant women. The improvement in the cases of colitis reported here compares favorably with the improvement in those uncomplicated by pregnancy. The reaction to pregnancy is variable. That some recover completely during the period of gestation is of particular interest. Could the variability in protein intake and absorption offer a lead to an explanation of this phenomenon? Perhaps the intestine acts as an organ of elimination of the excess products of protein metabolism. If this were so, the excess of protein in the body might in turn react favorably on the colitis. Under such circumstances we should expect no effects in some cases. An overwhelming infection might explain the fact that some cases actually become worse after pregnancy. It must be said that a further study of such cases might open up a fruitful field of investigation into both of these problems.

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In both urban and rural areas there is an evident increase in hospitalization of maternity cases. If this trend is due to a belief that the hospital is a safer place for delivery than the home, then we must insure the truth of that belief. We can do this by proper isolation of the maternity department in all of its ramifications. That will minimize infection contacts.

By proper organization of our staffs and facilities we can reduce the hazards of hemorrhage, and by consultation, the hazard of obstetric trauma and operative risk. By education of the public and profession we can reduce the convulsive toxemias of pregnancy. By staff conferences we can measure our organization and our results and effect changes to continue to make our hospitals worthy of the increasing confidence of our maternity patients.

J. P. GREENHILL.

# THE INHIBITION OF LACTATION DURING PUERPERIUM BY ANTERIOR PITUITARY AND OVARIAN EXTRACTS

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IT IS generally admitted that mammary growth and function are dependent upon hormones produced by the ovaries or by the anterior pituitary gland. A placental hormone also has been mentioned in this complex interrelationship. A delicate balance of hormonal stimulation and inhibition is important.

Kurzrok, Wilson, and Cassidy (1925) reported definite growth of the breasts by the use of large doses of follicular hormone. Vintenberger, Allen, Turner and others also found that estrone could stimulate growth of the mammary ducts, but they found that the corpus luteum hormone, progesterone, was necessary to bring about the hyperplasia of the lobules that also occurs during pregnancy. Nelson and Pfiffner in their experiments produced duct and lobule development with lipoid extract of sow's corpora lutea. Ancel and Bouin (1911), Lobe and Hasselberg (1917) and many others utilized aqueous lutein extracts without success.

It seems that if the aqueous ovarian extract of the whole ovary were used, one might obtain an antagonistic or galactophygous effect. For this purpose an ovarian extract* containing no estrone or other estrogenic substance was tried.

Realizing the part that the anterior pituitary gland plays in the regulation of ovarian activity, we decided also to use a preparation containing both ovarian and anterior pituitary extracts.† It was our expectation that the anterior pituitary extract would increase or heighten the response produced by the aqueous ovarian extract. In doing so, we were not unaware of the experiments of Pencharz and Long (1933), Stricker and Greuter (1929), Gardner and Turner (1933), Bates and Riddle, Kurzrok and others who established that certain anterior pituitary extracts were galactotropic.

Our results with anterior pituitary-ovarian solution to date, in conditions where the inhibition of lactation was desirable, have been extremely gratifying. In one group of 25 cases, aqueous whole ovarian extract alone was used. In another group of 75 cases, anterior pituitary-ovarian solution was used. The cases selected included: (1) mothers who had stillbirths of long or short duration; (2) mothers in whom the death of the fetus took place during labor; (3) mothers in whom an attempt at lactation was not advisable (i.e., those with deformed nip-

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*Supplied by the George A. Breon and Co. Each cubic centimeter contains the extractives from 40 gr. ovarian whole gland from cattle.

†Each 2 c.c. contains extractives of 10 gr. of anterior pituitary glands and 40 gr. of ovarian whole gland from cattle.

TABLE I. RESULTS IN 25 TYPICAL CASES

| CASE | PUERPERIUM DAY OF FIRST DOSE | NO. OF DOSES | PREPARATION | PARITY | DELIVERY | CHARACTER OF PUERPERIUM | RESULTS |
|---|---|---|---|---|---|---|---|
| 1 | 4 | 4 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Low forceps | Normal | All symptoms relieved after fourth dose |
| 2 | 1 | 4 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Cesarean section | Normal | No engorgement, no pain, no secretion |
| 3 | 1 | 4 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Normal | Normal | Breasts moderately full, but no pain and no secretion |
| 4 | 1 | 4 × 2 c.c. | Anterior pituitary-ovarian | iv | Version and breech extraction | Normal | No engorgement, no pain, slight secretion |
| 5 | 1 | 4 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Anencephalic monster | Normal | Breasts firm for 1 day, but no pain, no secretion |
| 6 | 6 | 4 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Normal | Normal | No engorgement, no pain, no secretion |
| 7 | 10 | 4 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Normal | Acute mastitis. Cracked nipples | Slight engorgement, pain decreased slightly, secretion stopped immediately |
| 8 | 2 | 2 × 2 c.c. | Anterior pituitary-ovarian | Primip. | Normal | Poor breast tissue. Normal | Complete cessation of secretion, no pain |
| 9 | 28 | 4 × 2 c.c. | Anterior pituitary-ovarian | ii | Normal | Cracked nipples, old scar and caked breasts | Immediate cessation of secretion, no pain |
| 10 | 1 | 3 × 2 c.c. | Anterior pituitary-ovarian | ii | Cesarean section. Placenta previa | Normal | No engorgement, no pain |
| 11 | 1 | 4 × 2 c.c. | Anterior pituitary-ovarian | i | High midforceps. Stillbirth | Normal | No secretion, no pain, no fullness |
| 12 | 5 | 4 × 2 c.c. | Anterior pituitary-ovarian | ii | Normal | Cracked nipples, caked breasts | Immediate cessation of pain, secretion and fullness |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13 | 2 | 4×2 c.c. | Anterior pituitary-ovarian | ii | Cesarean section. Placenta previa | Normal | No fullness, no pain, no secretion |
| 14 | 4 | 4×2 c.c. | Anterior pituitary-ovarian | iii | Premature, normal | Painful and engorged breasts. Normal | Pain and fullness decreased |
| 15 | 8 | 3×2 c.c. | Anterior pituitary-ovarian | i | Vaginal cesarean section | Engorged breasts. Acute mastitis | Pain disappeared, fullness decreased, secretion stopped |
| 16 | 1 | 3×2 c.c. | Anterior pituitary-ovarian | i | Stillbirth (3 weeks) | Normal | No fullness, no pain, no secretion |
| 17 | 1 | 3×2 c.c. | Anterior pituitary-ovarian | i | Low forceps | Normal | No fullness, no pain, no secretion |
| 18 | 1 | 2×2 c.c. | Anterior pituitary-ovarian | i | Stillbirth (6 months) | Normal | No fullness, no pain, no secretion |
| 19 | 1 | 4×2 c.c. | Anterior pituitary-ovarian | iii | Cesarean section | Normal | No fullness, no pain, no secretion |
| 20 | 1 | 4×2 c.c. | Anterior pituitary-ovarian | ii | Bougie induction for hemoptysis (T. B.) | Normal. Hemoptysis stopped | No fullness, no pain, no secretion |
| 21 | 5 | 4×2 c.c. | Anterior pituitary-ovarian | i | Low forceps | Caked breasts, cracked nipples | Immediate relief of pain and engorgement after first dose |
| 22 | 1 | 3×2 c.c. | Anterior pituitary-ovarian | Primip. | Twin delivery; 1st fetus 8 mo. premature; 2nd fetus dead and retained in uterus 1 mo. | Normal | No secretion, no pain, no fullness |
| 23 | 1 | 2×2 c.c. | Anterior pituitary-ovarian | i | Normal | Normal. Poor breast tissue | No secretion, no pain, no fullness |
| 24 | 1 | 2×2 c.c. | Anterior pituitary-ovarian | i | Low forceps rotation. R.O.P. | Normal | No secretion, no pain, no fullness |
| 25 | 4 | 4×2 c.c. | Anterior pituitary-ovarian | iii | Cesarean section. Placenta previa. Baby died on second day | Engorged breasts on fourth day | Immediate cessation of pain and secretion. Fullness for 2 days |

ples); (4) mothers in whom it was advisable to stop lactation because of the dangers of threatening breast abscess. (This last group included patients with intractably sore nipples, stubborn cases of caked breasts, and cases of acute mastitis.)

In order to fairly evaluate these preparations we insisted that no other method be used that might influence our results. For this reason, we did not bind the breasts tightly, use ice bags, saline cathartics, sedatives, or restrict fluids in any of our cases.

Our treatment consisted of daily intramuscular injections of 2 c.c. of the respective extract on the first, second, third, and fourth days following delivery. In only one case was it necessary to give a fifth injection.

In the anterior pituitary-ovarian treated group, our results were good in 70 cases, fair in 3, and ineffective in 2. In the ovarian treated group (25), good results were obtained in 17 cases, fair in 5, and no effect was noted in 3 cases. It seemed that in the ovarian treated cases the amount of fullness of the breasts was a little more marked. Our observations in the anterior pituitary-ovarian series were as follows: (1) In no case was it necessary to give analgesic drugs to stop pain. (2) The nurses reported that none of these patients required help in turning because of engorged breasts. (3) The breasts were not as hard and as tense as they were under the old regime of ice bags, restricted fluids, saline cathartics, and breast binders. (4) The temperatures from engorged breasts were entirely absent. (5) No patient complained so severely that additional support of the breasts was necessary. (6) In two cases the breasts became full but the freedom from pain was remarkable.

The result on 25 typical cases are summarized in Table I.

This regime was used in three different hospitals by 15 unbiased clinicians. All observers spoke highly of this method; some stating that their results were excellent.

### SUMMARY

No single preparation can be depended upon to give uniformly excellent results in bringing about a painless cessation of lactation. The combined extracts of the anterior pituitary and ovarian glands of cattle gave excellent results in at least 90 per cent of those treated. The results in a group of patients treated with ovarian extract alone were not as satisfactory as in the anterior pituitary-ovarian group, good results being obtained in only 68 per cent of the cases. While some engorgement of the breasts was noted in a few of the patients treated by these preparations, the freedom from pain is a prominent feature.

517 ROSEVILLE AVENUE

# THE LONGEVITY OF THE HUMAN SPERMATOZOA

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THE mass of evidence showing that the spermatozoa of animals with extra-abdominal testes live but a relatively short time (forty-eight hours or less) at body temperature, and therefore an equally short time in the female genital tract, has assumed enormous proportions and is steadily increasing. Here and there, however, a dissenting voice is heard.

Huhner[1] reports taking sperms from the cervix many days after coitus and finding them motile under the microscope. Macomber[2] reports similar findings four and even seven days post-coitum, and Carey[3] reports progressively motile sperms removed from the cervix thirty-six to eighty hours after coitus. Carey also cites Stokes'[4] experiences after vasectomy and Nürnberger's[5] cases which he reported eighteen years ago in which the excised Fallopian tubes thirteen and fourteen days after the last reported (!) intercourse showed motile spermatozoa.

Of course patients often unconsciously and deliberately deceive their physicians in this question, but both Huhner and Carey, feeling that this was not true in their reported cases, think that their findings are a contradiction of the fact that sperms live but a short time in the female genital tract. The findings of these authors are however not at all at variance with the modern scientific view, but one must specify what is meant when one says that all the sperms are killed in the female genital tract in forty-eight hours or less. This statement of course applies to such sperms as are possibly concerned in fertilizing the ovum and meet normal conditions in the female genital tract. That some sperms may meet unusual conditions, or may be too weak to penetrate the cervical mucus is of no importance in this question, and certainly sperms still in the cervix after two to seven days have not met normal conditions, or are inherently abnormal in one way or another. To make this point clear, it is necessary to review our present knowledge of spermatogenesis as briefly as possible.

The sperms produced by the testes when they become free-swimming have a sluggish motility and are not mature. As they move along the rete and vasa deferentia to the epididymis they mature and become increasingly motile. This process continues until the sperms reach the tail of the epididymis. Here they are packed in like sardines and due to the lack of oxygen and the strongly alkaline secretion of the epididymis remain practically motionless. (The sperms are not stored in the seminal vesicles as was formerly believed. This I have pointed out repeatedly before.) Sperms taken from different parts of the ducts always exhibit varying degrees of motility depending on how far along the ducts they have journeyed. Even stimu-

lants of motility, such as glucose solution or Hirokawa's diluent (one part of 1/10 N sodium chloride solution and 100 parts of Ringer's solution) will not change the relation of their various motilities. Again, sperms deprived of oxygen are only sluggishly motile and lose practically all motility in a $CO_2$ environment.

It is evident that in the sperm reservoir of the male, that is, the epididymis, the sperms must be able to live for many days.

Hammond and Asdell[6] have shown in the rabbit after isolation of the tail of the epididymis sperm survival with retention of their fertilizing powers up to 40 days, and retention of motility up to 60 days. Young[7] found that under similar conditions in the guinea pig the spermatozoa retained their fertilizing powers for 25 to 30 days and their motility for 50 to 59 days, while White's[8] figures in rats were 21 and 42 days, respectively. However, the epididymis in the scrotum is at a lower temperature (2.5 to 7° C.) than the body itself, and when the gonads and epididymis are transplanted into the abdominal cavity, degeneration of the testicular tubules results and any form of heat whatever applied to the testes for any length of time has the same effect. Even the process of wrapping the scrotum in some impermeable substance like oiled silk will cause testicular tubular degeneration. However, the spermatozoa in the tail of the epididymis survive this heat insult much better than the testicular tubules. Thus, bathing the scrotum of a guinea pig with water at 46° C. for 30 minutes produced a severe testicular tubular degeneration, whereas the sperms in the epididymis remained fertile for 31 days afterward. Lawrence,[9] Moore,[10] Heller,[11] and Yochem[12] have shown that sperms in the scrotum of a guinea pig remained motile for 70 days and only 14 days in the abdomen. In the rat the figures were 30 days and 5 days, respectively.

Outside of the body the sperms of course live a much shorter time. At body temperature Hammond,[13] Walton,[14] and Hammond and Asdell[15] showed that rabbit sperms remained fertile only 13 to 14 hours. The sperms lived longest at 10° to 15° C., and even at 0° C. some lived 72 hours. Sperms taken from the vas deferens if kept cold could be kept fertile for as long as 7 days, whereas those from the vagina never more than 4 days. I myself have divided the same human serum ejaculate into three parts and kept all three parts under identical conditions, except that one was subjected to normal body temperature in the incubator, one was left at room temperature, and one was placed in the refrigerator at 10° C. All the incubator sperms were dead after 18 hours. Those at room temperature lasted about 36 hours (summer weather), and those kept in the ice box four to five and more days.

The obvious conclusions from the foregoing are that the sperms mature as they move along the tubular system of the testicle, rete, vasa deferentia and epididymis; that they are stored more or less immobile in the epididymis under a lack of oxygen and held in check further by strongly alkaline secretions; that the temperature is regulated by the scrotum and is always lower than the general body temperatures; that body temperature reduces the life of the sperms 75 to 90 per cent, and that the more mature the sperms, the sooner they die; that ejaculated spermatozoa in all animals investigated die in less than 48 hours when exposed to body temperature, providing oxygen is available; that the sperm withstands heat better if there is

a lack of oxygen and strong alkaline buffering secretions surround them; that motility is not a criterion of the fertilizing power of the sperm cell, and that motility is generally retained for a considerably longer period of time than fertilizing power.

If in this light we now consider the reports of Huhner, Carey and Macomber, it will be seen that sperm cells embedded in the cervical mucus will be suspended in a strongly alkaline medium, while little oxygen is available. Their motility therefore will necessarily be reduced or almost nil, as in the epididymis a potential motility may remain for days. When such sperms are placed under the microscope and oxygen becomes available they naturally may show active motility. That does not mean, however, that such cells are still fertile, and it certainly means that something is radically wrong; otherwise these sperms would be through the cervical mucus, not in a few days, but in a few hours. These reported sperm findings in the cervix after such long intervals post-coitum therefore are simply freaks which in no wise modify the well founded conclusion that the sperms (those to be considered as possibly causing pregnancy, if one wishes) are all killed off by the heat and environment of the female genital tract in less than 48 hours. Since in all experiments the sperms taken from the vagina always lived only about half the time of those from the vas deferens and the tail of the epididymis, the conclusions are obvious; namely, to evaluate properly the quality of a semen specimen it must not be taken from the vagina or cervix, but must be a fresh ejaculate kept cool. Of course if a condom is used, prompt removal from the condom should take place immediately after ejaculation, and preferably the condom should be held up and its closed end snipped with a scissors so that the semen comes into contact with as little rubber surface as possible, or a skin condom may be used. And even then a complete evaluation of a semen specimen can only be made if all the factors influencing spermatogenesis are thoroughly known and properly considered.

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40 WEST 55TH STREET

# TEN CASES OF BRENNER TUMOR OF THE OVARY

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THE tumor is rare so far as reports in the literature are concerned, but all writers agree that it is only moderately so if routine gross and microscopic section of the ovary is performed. Bland and Goldstein[2] reported 66 cases in the literature to 1935, but since the indefinite terminology and the heretofore confusion with granulosa cell tumors and simple carcinoma make it quite probable that not all these cases were true Brenner tumors, the 24 cases to 1936 gathered by Proescher and Rosasco[3] may represent a truer picture. In addition, the following have recently published 11 cases: Frankl and Klatten[4] in 1934, 1 case; P. H. Smith[5] in 1935, 1 case; Sikl[6] in 1935, 2 cases; Bassal and Fabre[7] in 1936, 1 case; Gaines[1] in 1936, 4 cases; Proescher and Rosasco[3] in 1936, 1 case; and Gnassis[8] in 1937, 1 case.

The first seven of our ten cases were found by re-examination of all the microscopic sections of ovary in the pathologic files (since 1901, by G. V. S.), and the diagnosis was confirmed through the courtesy and cooperation of Dr. Robert Meyer, of Berlin, in 1934. Of these 7 cases 1 had been completely missed, 1 had been termed a fibroma, another simply "gland inclusions"; 2 had been diagnosed as early carcinoma, 1 as a fibrosarcoma, and 1 as a granulosa cell tumor. The last 3 cases encountered, since the consultation with Dr. Meyer, have been diagnosed without hesitation.

Table I graphically summarizes the findings, but the following facts deserve further note, though they have been mentioned in previous papers. Six of the 10 tumors were associated with cysts on the same and/or opposite side, and of these, 3 were benign multilocular pseudomucinous cystadenomas, 2 benign papillary serous cystadenomas (one early), and 1 was cortical, i.e., the ovary contained many cortical glands, some cystic. The apparently incidental finding of a Brenner tumor in a case of squamous carcinoma of the vagina with procidentia was the only instance of association with malignancy in this series; no other indication of or association with malignancy has been found or published. Six of the remaining 9 tumors were also microscopic and entirely incidental, 1 being found in the wall of a multilocular pseudomucinous cyst; 3 were grossly the apparent pathology, being solid ovarian tumors 2 by 2 by 2, 7 by 5 by 5, and 10 by 8 by 6 cm. in diameter, respectively. Leiomyomas of the uterus were present in 5 cases; adenomyosis in 3. Three patients had had pelvic inflammatory disease but only 1 had known latent syphilis. Two patients were in the fourth decade, 4 in the fifth, 1 in the sixth, and 2 in the seventh. Two cases were postmenopausal without bleeding, 2 (1 with squamous carcinoma of the vagina, the other with polyps) were postmenopausal with recent spotting, 1 was without history, 1 had normal menses, and 4 had moderate to profuse increase of menstrual flow. All (9, one clinical history unobtainable) except 2 had had one or more children and both of these had had spontaneous abortions.

## CASE REPORTS

CASE 1.—Mrs. L. was operated upon on March 21, 1910. The patient was a private case and the clinical record is not available.

*Pathologic Report No. 2468, Gross:* The specimen consisted of a multilocular ovarian cyst 18 by 17 by 6 cm. without papillary formations. *Microscopic:* Sections of the cyst wall showed a high cylindrical epithelium in a single layer. In dense ovarian stroma there were several nests and islands of polygonal epithelial cells showing no signs of infiltration. A few of these nests were vacuolated to varying

TABLE I. CONDENSED DATA CONCERNING TEN CASES OF BRENNER TUMOR OF THE OVARY

| PATIENT HOSPITAL NO. PATHOLOGY NO. | AGE | GRAVIDA | PARA | YEAR | PREOPERATIVE DIAGNOSIS | SIZE OF BRENNER TUMOR | ASSOCIATED PATHOLOGY | ORIGINAL DIAGNOSIS | FOLLOW-UP |
|---|---|---|---|---|---|---|---|---|---|
| 1. Mrs. L. Private case 2468 | ? | ? | ? | 1910 | Ovarian cyst | 3 mm. in wall of ovarian cyst | Pseudomucinous cystadenoma 18 by 17 by 6 cm. | Missed | ? |
| 2. Mrs. C. S. 28-59 7007 | 41 | 1 | 1 | 1917 | Prolapse | 2 cm. nodule, left ovary | Calcification of left ovary | Fibroma of ovary | Well 11 yr. P.O. |
| 3. Mrs. G. P. 44-75 14567 | 45 | 1 | 0 | 1927 | Pelvic inflam.; rt. inguinal hernia | Microscopic | Fibroids; inflammation; many cortical glands, some cystic, in other ovary | Gland inclusions | Well 7½ yr. P.O. |
| 4. Mrs. E. A. C. 46-210 16001 | 49 | 3 | 2 | 1928 | Prolapse; recto-vag. fistula | 1.5 cm. inside right ovary | Fibroids; discrete adenomyoma; fistula-in-ano | Atypical carcinoma | Well 7 yr. P.O. |
| 5. Mrs. E. J. W. Private 1992 15362 | 66 | 5 | 4 | 1927 | Ovarian cyst | 10 by 6 by 8 cm. left ovary | Endometrial and cervical polyps; diffuse adenomyoma; pseudomucinous cystadenoma, 20 by 17 by 13 cm., rt. ovary | Fibrosarcoma with epithelial inclusions | Well 3 yr. P.O. |
| 6. Mrs. A. L. C. 20940 19093 | 68 | 5 | 4 | 1931 | Procidentia with ulceration | 0.5 cm., left ovary | Endometrial polyp; squamous cell carcinoma of vagina | Early carcinoma | Died 3 yr. P.O.—circulatory death |
| 7. Mrs. L. L. 22818 21013 | 39 | 6 | 5 | 1932 | Comp. lac. of perineum; fibroids | 7 by 5 by 5 cm., right ovary | Fibroids; diffuse adenomyoma; inflammation | Granulosa cell tumor | Well 3½ yr. P.O. |
| 8. Mrs. M. L. R. 26485 25495 | 44 | 1 | 2 | 1935 | Ovarian cyst | Microscopic, left ovary, with early pap. serous cystadenoma | Multilocular pseudomucinous cystadenoma, 18 cm., right ovary | Brenner tumor | Well 1 yr. P.O. |
| 9. Mrs. A. L. W. 28867 28825 | 37 | 1 | 0 | 1937 | Fibroids | Microscopic | Fibroids; inflammation | Brenner tumor | Well 6 mo. P.O. |
| 10. Mrs. E. C. S. 29229 29373 | 51 | 3 | 2 | 1938 | Ovarian cyst | Microscopic, right ovary | Fibroids; papillary serous cyst-adenoma, left ovary | Brenner tumor | Well 3 mo. P.O. |

degrees. *Diagnosis:* Multilocular pseudomucinous cystadenoma. This was later changed to include Brenner tumor and was confirmed by R. Meyer in 1934.

CASE 2.—Mrs. C. S., a 41-year-old white female, gravida i, para i, was admitted to the hospital on May 24, 1917, complaining of a bearing-down sensation in the vagina, pain in the left lower abdomen and lumbar backache, all symptoms having been present an indefinite time but worse in the past four months. The menstrual history was normal but the abdominal pain was exacerbated during menstruation. Pelvic examination revealed a cystocele, lacerated cervix, prolapse, fundus forward and of normal size, a tender mass in the left adnexal region, and the right adnexal region negative. Dilatation and curettage, anterior colpoplasty, perineoplasty, left salpingo-oophorectomy, appendectomy and fixation of the round ligaments were done. The patient reported herself well eleven years later.

*Pathologic Report No. 7007:* The curettings were grossly normal. The ovary measured 5 by 2 by 2 cm.; at one end there was a nodule 2 centimeters in diameter which appeared to be a fibroma. The endometrium was of the pre-menstrual type. The ovary showed the usual structure of a fibroma and scattered through it were small nests of epithelial cells with a few areas of calcification. *Diagnosis:* Pre-menstrual endometrium; fibroma of ovary, normal appendix.

The diagnosis of fibroma was later changed to that of Brenner tumor and this was confirmed by R. Meyer.

CASE 3.—Mrs. G. P., a 45-year-old white female, gravida i, para none, entered the hospital Feb. 14, 1927, complaining of left lower abdominal pain, increased with catamenia and associated with a bearing-down sensation, for one year and of a small, tender lump in the left groin for six months. The menstrual flow had been irregular and heavy for five years. Examination revealed an enlarged external inguinal ring on the right, the uterus forward and an irregular, nontender mass behind the uterus. A dilatation and curettage, bilateral salpingo-oophorectomy and supravaginal hysterectomy were performed. The patient was in good health seven and one-half years later.

*Pathologic Report No. 14567, Gross:* The specimen consisted of a multiple fibroid uterus with tubes and ovaries attached, the fibroids measuring up to 10 by 6 by 5 cm. The right ovary was atrophic, the left ovary cystic and slightly enlarged. *Microscopic:* The myometrium was normal; the glands of the endometrium were hypertrophied. Both tubes showed thickening of the walls and villi with round cell infiltration. One ovary showed fibrosis and a number of gland inclusions; the other contained many cortical glands, some cystic. *Diagnosis:* Multiple fibromyoma with chronic salpingitis and oophoritis.

On re-examination later the gland inclusions were found to be nests of epithelial cells of a one-millimeter Brenner tumor. This diagnosis was confirmed by R. Meyer.

CASE 4.—Mrs. E. A. C., a 49-year-old white female, gravida iii, para ii, entered the hospital June 7, 1928 complaining of passage of fecal material through the vagina, a ''falling out'' sensation in the vagina and occasional increased menstrual flow. Twenty-one years before she had had a dilatation and curettage, a resection of the right ovary, a left inguinal herniorrhaphy and a fixation of the round ligaments. The pathologic diagnosis was cystic degeneration of the ovary. At this second entrance, pelvic examination revealed a rectovaginal fistula, cystocele, rectocele, and prolapse. A dilatation and curettage, amputation of the cervix, anterior colporrhaphy, appendectomy, bilateral salpingo-oophorectomy and supravaginal hysterectomy were done. She was in good health seven years later.

*Pathologic Report No. 16001, Gross:* The uterus and cervix were normal except for a 1 cm. fibroid on the anterior wall of the fundus. On sectioning the right ovary a solid nubbin 1.5 cm. in diameter was found in the center. The left ovary contained a 2 cm. corpus luteum cyst. *Microscopic:* The myometrium and endometrium were normal. The fibroid showed hyaline change. The right ovary contained a small amount of normal stroma surrounding a mass of bundles of fibrous tissue, scattered between which were areas of epithelioid proliferation. Some of these areas contained lumens. There was no evidence of invasion or metastases. *Diagnosis:* Fibromyoma with hyaline degeneration, atypical carcinoma of the ovary (right) and discrete adenomyoma of the posterior surface of the fundus.

The diagnosis of atypical carcinoma was later changed to that of Brenner tumor, and this was confirmed by R. Meyer.

CASE 5.—Mrs. E. J. W., a 66-year-old white female, gravida v, para iv, entered the hospital on Nov. 21, 1927, complaining of slight bleeding for one week. The menopause had occurred sixteen years previously and there had been no bleeding until the present illness. Pelvic examination revealed an irregular, nodular, cystic mass reaching to the umbilicus, a rectocele, cystocele, and laceration of the cervix. A dilatation and curettage, cauterization of the cervix, bilateral salpingo-oophorectomy and supravaginal hysterectomy were performed. The patient was in good health three years later.

*Pathologic Report No. 15362, Gross:* The specimen consisted of a multilocular, bluish-white, right ovarian cyst, 20 by 17 by 13 cm., containing slimy, yellow fluid. In one region the wall was thickened and indurated and on section had the appearance of beginning malignancy. There was a cervical polyp 2 by 1 by 1 cm. On opening the normal-sized uterus, a mucous polyp 5 by 3 by 3 cm. was found. The left ovary was solid, white and nodular, measuring 10 by 6 by 8 cm.; on section, several 1 to 2 cm. cystic areas were found. *Microscopic:* The cervical and endometrial polyps showed no malignant changes. The myometrium contained a few glandular areas. The ovarian cyst showed tall, columnar epithelium lining cavities. The stroma of the left ovary was dense and fibrous, containing peculiar cellular areas with occasional central necrosis. Neither mitoses nor invasion was found but the appearance was that of sarcomatous degeneration. *Diagnosis:* Atrophic endometrium with adenomyosis of uterine wall, endometrial polyp, cervical polyp, pseudomucinous cystadenoma of right ovary and fibrosarcoma with epithelial inclusions and necrosis of left ovary.

This diagnosis was later changed to Brenner tumor and confirmed by R. Meyer.

CASE 6.—Mrs. A. L. C., a 68-year-old white female, gravida v, para iv, was admitted on June 1, 1931, complaining of a protrusion from the vagina for one year and of slight staining from an ulceration of the protrusion for five weeks. Twelve years prior to this second admission she had had a repair of an umbilical hernia, a multiple myomectomy, and a fixation of the round ligaments with successful result. The menopause had taken place fourteen years before and there had been no bleeding until the present illness. Pelvic examination revealed a procidentia with an ulcerated, thickened area of the vagina near the cervix. An anterior colporrhaphy, excision of ulcer, and application of radium were performed. One month later, amputation of the cervix, excision of the ulcerated area, bilateral salpingo-oophorectomy, and supravaginal hysterectomy were carried out. The patient was in a good condition when seen two years postoperatively but died of circulatory failure three years postoperatively.

*Pathologic Report No. 19093, Gross:* The cervix was without visible evidence of malignancy. A 5 by 4 cm. portion of vaginal mucous membrane had a hard, ulcerated crater in the center. Both tubes and the left ovary were normal. The uterus contained an endometrial polyp. The right ovary was enlarged to 6 cm. by several cysts which showed no papillary ingrowths. *Microscopic:* The myometrium was fibrotic and contained a small fibroid; the endometrium was atrophic. The squamous epithelium of the cervix was thickened and there was round cell infiltration. The ulcerated area of vaginal mucous membrane showed, first, a layer of radium slough, then chronic inflammation and then an area of scattered alveoli with strands of active squamous cell carcinoma. The left ovary was atrophic but contained a few areas of epithelial proliferation scattered in a dense stroma; neither mitosis nor infiltration was found in these areas. *Diagnosis:* Squamous carcinoma of the vagina; retention cysts of the right ovary; endometrial polyp; early carcinoma, left ovary.

The diagnosis of early carcinoma was later changed to Brenner tumor and confirmed by R. Meyer.

CASE 7.—Mrs. L. L., a 39-year-old white female, gravida vi, para v, entered the hospital on Nov. 7, 1932, complaining of fecal incontinence for five years, right

lower abdominal pain for one year and increased menstrual flow for two months. Examination revealed a complete laceration of the perineum, a lacerated cervix, and a mass on the right side attached to the uterus. Dilatation and curettage, biopsy and cauterization of the cervix, bilateral salpingo-oophorectomy and supravaginal hysterectomy were effected. The patient was in good health three and one-half years later.

*Pathologic Report No. 21013, Gross:* The curettings were hyperplastic. The tubes were normal. The uterus had a 2 cm. fibroid in the fundus. The left ovary measured 3.5 cm. and contained a follicle cyst. The right ovary measured 7 by 5 by 5 cm. and was firm and fibrous throughout. *Microscopic:* Sections of the cervix showed chronic inflammation. The fibroid showed no malignant changes; the tubes and left ovary were normal. The right ovary consisted of bundles of fibrous tissue showing hyaline changes and scattered, irregular, small masses of epithelial cells with occasional central necrosis. The stroma of the endometrium was dense; the glands were hyperplastic and a few were dilated. There were a few endometrial glands within the myometrium. *Diagnosis:* Endometrial dysplasia; diffuse adenomyoma of the uterine wall; chronic cervicitis; fibromyoma; granulosa cell tumor of the right ovary; bilateral perisalpingitis.

A diagnosis of Brenner tumor was made later and confirmed by R. Meyer.

CASE 8.—Mrs. M. L. R., a 44-year-old white female, gravida i, para ii (twins), entered the hospital Dec. 12, 1935, complaining of abdominal swelling for eight months and of occasional urinary incontinence for many years. The menses had been normal until the menopause six years before entrance and there had been no bleeding since. Abdominal and pelvic examination revealed a cystic tumor filling the lower abdomen; the uterus was of normal size and mobility. Dilatation and curettage, cauterization of the cervix, supravaginal hysterectomy and bilateral salpingo-oophorectomy were performed. She was well one year later.

*Pathologic Report No. 25495, Gross:* The specimen consisted of a multilocular cyst 18 cm. in diameter containing clear, stringy, mucoid fluid and of an atrophic uterus. The left ovary was fibrosed and atrophic. *Microscopic:* The myometrium and endometrium were atrophied. The cyst of the right ovary was lined with tall, columnar epithelium secreting mucus. On the surface of the left ovary were several areas of beginning papillary growth covered with flat to cuboidal epithelium; from these areas epithelial-lined crypts dipped down into the ovarian stroma. In the cortex of this ovary were a number of well-circumscribed islands of epithelial cells, several of which contained a central vacuole. *Diagnosis:* Atrophy of tubes, myometrium and endometrium; multilocular pseudomucinous cystadenoma, right ovary; beginning papillary serous cystadenoma and Brenner tumor of left ovary.

CASE 9.—Mrs. A. L. W., a 37-year-old negress, gravida i, para none, entered the hospital Nov. 1, 1937, complaining of a gradual enlargement of the abdomen for one year and of abdominal pain for one week before menses for three months. Menses had been regular but more profuse during the past year. The Wassermann reaction was positive. Abdominal and pelvic examination revealed an irregular, nodular tumor arising in the pelvis and extending to the epigastrium. Lysis of omental adhesions, supravaginal hysterectomy, bilateral salpingo-oophorectomy and appendectomy were done. The patient was well six months after operation.

*Pathologic Report No. 28825, Gross:* The uterus was enlarged and nodular, measuring 15 by 14 by 14 cm., and had one pedunculated fibroid measuring 27 by 19 by 19 cm. The tubes and ovaries were normal. *Microscopic:* In one ovary was an area consisting of dense fibrous stroma with numerous small masses of epithelial cells which were well differentiated and showed no evidence of malignancy. *Diagnosis:* Normal endometrium; submucous and pedunculated leiomyomas; normal ovary; Brenner tumor of ovary.

CASE 10.—Mrs. E. C. S., a 51-year-old white female, gravida iii, para ii, entered the hospital Feb. 12, 1938, complaining of a gradually enlarging abdomen associated with lumbar backache for three years. Menses had been regular until the menopause five years previously and there had been no bleeding since. A dilata-

tion and curettage, removal of cysts of one ovary and an appendectomy had been performed elsewhere fifteen years before; a cholecystectomy had been done eight years before. Dilatation and curettage, supravaginal hysterectomy, left salpingo-oophorectomy and right salpingo-oophorectomy were performed. Three months later the patient was in good health.

*Pathologic Report No. 29373, Gross:* The uterus measured 5 by 5 by 3 cm. and there was a 1 cm. pedunculated fibroid at the right cornu. The right ovary and both tubes were atrophic. The left ovary was replaced by a multilocular serous cyst 15 cm. in diameter, containing a few papillary projections. *Microscopic:* In the right ovary was a 4 mm. nodule at one pole consisting of fibrous tissue with small islands and strands of pavementlike epithelial tissue without evidence of malignancy. *Diagnosis:* Atrophic endometrium; leiomyoma; atrophic ovary with Brenner tumor, right; benign papillary serous cystadenoma, left ovary.

### SUMMARY

Ten cases of Brenner tumor of the ovary have been presented, the diagnosis of seven of which has been confirmed by R. Meyer. The clinical and pathologic findings have been summarized and briefly discussed.

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# ENDOMETRIAL BIOPSY AND THE UTERINE INDEX

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THIS report is a description of two instruments used in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital to determine uterine development and to obtain endometrial biopsies.

During the past five years the Pathology Department of the Massachusetts General Hospital has examined 1,500 pieces of tissue removed from the endometrial cavity. These specimens are part of a study being carried out upon patients with amenorrhea, dysmenorrhea, sterility, and abnormal uterine bleeding. The value derived is great and later a detailed report will be presented of the pertinent facts obtained. It is essential in gynecologic endocrine studies to know whether or not a given piece of endometrium agrees with the day of the menstrual cycle and whether the patient has ovulated or not. In a report written in 1936, Sturgis and Meigs described the various stages of the endometrium, and this same scheme for "dating" has been followed since. Later studies have convinced the authors that much more material must be viewed before accurate dating can become a certainty. There are many specimens that do, but many specimens do not coincide with the date of the cycle. It is likely that the end organ (uterus and endometrium) is important and that this organ may not respond perfectly to its ovarian stimulation. There may be underdevelopment of the uterus so that its indicator (the endometrium) cannot respond as it should. It is obvious that a method of measuring the proportionate size of the uterus must be developed if endocrine studies are to be carried out in addition to a method of obtaining tissue from the endometrial cavity.

In his book *Human Sterility* (Williams and Wilkins Company, 1934), S. R. Meaker describes his method of obtaining a "uterine index." This index is an indicator of the proportionate development of the cervix and uterus. It has been long recognized

that the proper normal adult proportion of the body of the uterus to the cervix is as 2 to 1, and that the measurement of the true infantile uterus is as of 1 to 2. There are various other proportions, the most important of which is the juvenile with the cervix and body of equal length. Meaker introduced a hysterometer to measure and a formula to give a number or "index" as an expression of normal or abnormal development. If the cervix measures 3 cm. and the whole uterus from cervix to the top of the fundus 9 cm. then the proportions are proper, that is, 6 cm. or 2 for the body and 3 cm. or 1 for the cervix. He has set arbitrary limits for his index and anything above 0.75 indicates normality and anything below 0.60 represents definite hypoplasia. In dealing with amenorrhea, sterility, etc., knowledge of this "index" is of great importance. The formula is as follows:

$$\frac{1}{2} \cdot \frac{\text{(uterus minus cervix)}}{\text{cervix}}$$ equals the index. Placing the above figures in the formula $\frac{1}{2} \cdot \frac{(9\text{-}3)}{(3)}$ or $\frac{1}{2} \cdot \frac{(6)}{(3)}$ or $\frac{1}{2}(2) = 1$ the index for the normal. These figures represent the perfectly developed uterus. If the cervix should measure 4 cm. and the whole uterine cavity from cervix to fundus 8 cm., the formula would be as follows:

$$\frac{1}{2} \cdot \frac{(8\text{-}4)}{(4)}$$ and the result 0.5, which would be an indication of underdevelopment. If the cervix should be longer, let us say 4 cm., as it is in the infantile uterus the calculation $\frac{1}{2} \cdot \frac{(6\text{-}4)}{(4)}$ would give 0.25, an indication of real underdevelopment. His instrument or hysterometer has been redesigned and is illustrated in Fig. 1, $A$ and $B$. This instrument is an ordinary uterine sound measured off into centimeters. A finely coiled spring is used as part of the apparatus so that the sliding part can negotiate the curve of the sound. The instrument is introduced into the cervical canal and when obstruction is met (at the internal os) the measurement is read at the proximal end of the sliding portion. This is recorded as 3 cm. or 4 cm., or whatever it reads. Then without withdrawing the instrument, for the reading is easy, it is advanced into the uterine cavity until it reaches the top of the fundus when another reading is made, for instance 7 cm. or 8 cm. These two measurements which represent the length of the cervix and the length of the entire uterus are then incorporated into the formula and the index obtained. Usually it is only necessary to think of the proportions and an index of the proper or improper development is immediately suggested. For example, if the cervix measures 3 cm. and the uterine cavity 9 cm., it is obvious that the body measures 6 cm. and the cervix 3 cm. and that therefore the proportions are adult normal.

Before inserting the probe the vagina must be cleaned out and the cervix painted. Usually the cervix is caught with a uterine tenaculum to hold it steady as in doing a dilatation, but occasionally both an "index" and a biopsy may be obtained without a tenaculum, the instruments passing easily by the internal os and into the uterine cavity.

In the early days of the clinic the Burch punch (Pilling) was used to obtain biopsy specimens because it was felt that with this instrument a piece could be removed from any part of the cavity desired. Because of the expense of the apparatus and the difficulty in keeping it in perfect working order it was discarded. Later a suction curette was used but the necessity for another pair of hands to maintain the suction, and because of the occasional plugging of the instrument with dried blood, it was given up. It then occurred to me that it would be easy to cup the knob on the end of the hysterometer and to use it to obtain specimens at the same time the uterine index was being made. This was done and proved useful. However, on occasions it was found that the cup of the curette caught at the internal os while being removed and made the biopsy painful, so that a smaller curette (Fig. 1, $C$) was made. The cup of the small curette has a small hole bored in the top to let out any secretions (blood, etc.) that may get in. After the hysterometer has

been passed it is easy to insert the curette because its cup is smaller than the knob on the end of the sound. Thus after the sound has been passed, the direction of the canal is obvious and the curette follows easily. It is frequently unnecessary to use a tenaculum, thus relieving the patient of a somewhat uncomfortable sensation when the cervix is caught.

It is almost impossible to insert this curette into the uterine cavity and withdraw it without obtaining a perfectly adequate specimen from the endometrium. Its method of use is illustrated in Fig. 1, *D*, showing the curette beyond the internal os and in the uterine cavity. A slight pressure is made on one side and then it is turned around, and a similar pressure made on the other side, assuring two pieces of tissue. We have rarely found that these two pieces of tissue vary microscopically and do not believe it is necessary to strip the endometrium with the idea that many
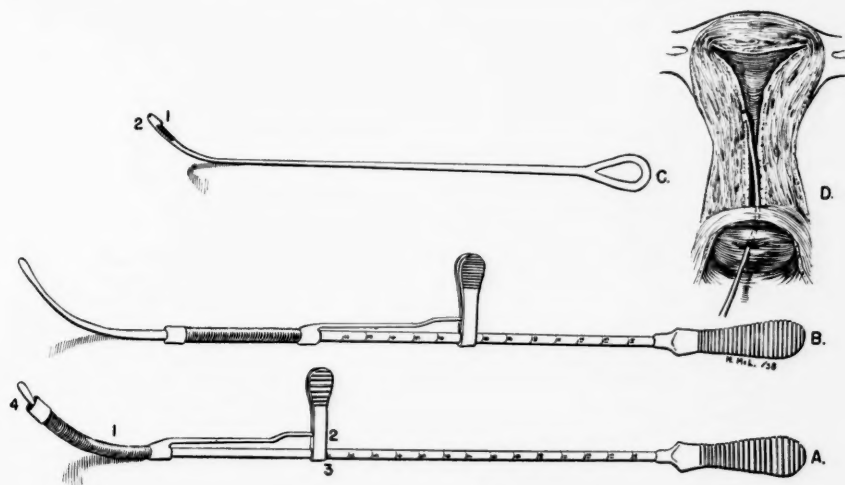


Fig. 1.—*A*, Hysterometer. *1.* Coiled spring so that the curve of the sound may be passed; *2.* spring clip which is used as a handle to move the measuring part of the apparatus and to hold it steady on the shaft; *3.* area of measurement. Notice it registers 1 cm. and there is 1 cm. at *4.* *B.* Showing the hysterometer measuring 7½ cm. as it would if the curved part were in the uterine cavity. *C.* Small steel cupped curette. *1.* Sharp overhang to curette; *2.* small hole in cup to allow escape of secretions. *D.* Curette removing tissue from the endometrium. The curette can be used numerous times to obtain tissue from different regions but a piece from either side is usually sufficient. These instruments are made by Codman and Shurtleff, Boston, Mass.

different types of endometrium may be found. It is well known that the endometrium just above the internal os is different and that it is not as responsive to hormones as the upper part of the endometrium, but if the curette is placed high in the cavity, good specimens of active endometrium are easily obtained. The specimens are removed from the cup of the curette with fine splinter forceps and are placed in Zenker's solution immediately. They are then cut in paraffin and stained with hematoxylin and eosin. Zenker preserved tissue gives better detail than formalin preserved tissue.

The trauma associated with passing the hysterometer, the curette, and the biopsy itself causes a moderate amount of pain similar to a uterine cramp. After a few minutes it passes away and the patient leaves the clinic without discomfort. The patient should be told that a dribble of blood may follow the biopsy for from two to four days and that this should not be misconstrued as a period. The patient on leaving is given a return postal card upon which to indicate the date of onset of her period following the biopsy. It has been noticed occasionally that if the biopsy is done near the time of an expected menstruation, the flow may be started and a true catamenia ensues.

Occasionally in patients with amenorrhea or prolonged bleeding it is difficult to obtain tissue with the sharp curette. It is then necessary to use the Burch punch to really "bite" out a piece of uterine wall with its very thin layer of endometrium.

The methods described above for obtaining an endometrial biopsy and the uterine index have been in use in our clinic for five years, and after removing more than 1,500 specimens from the uterus without any disasters, we feel that it has proved to be satisfactory, simple, inexpensive, and safe. Although a few specimens have shown unmistakable evidence of early pregnancy, only one patient has miscarried, and this was a sterility patient who had had two weeks of dribbling and probably was about to miscarry spontaneously.

In studying patients with endocrine disorders and sterility, endometrial biopsy must be done and the uterine index found, but it is very important to emphasize that this method of biopsy cannot be used to exclude cancer of the body and endocervix. In a suspected case a real curettage of the whole uterine cavity should be carried out.

### CONCLUSIONS

1. A method is described for obtaining endometrial biopsies and for measuring the proportions of the uterine cervix and body.

2. The method has been in use in the Ovarian Dysfunction Clinic of the Massachusetts General Hospital for over five years, and in no patient has any serious difficulty or sequela occurred.

3. The use of these two methods of investigation are recommended in the study of endocrine and sterility problems, but the method will not replace careful curettage in patients with suspected tumors of the inside of the uterus.

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# ASYMPTOMATIC AXIAL ROTATION OF A FULL-TERM UTERUS THROUGH 180 DEGREES

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*(From the St. Vincents Hospital)*

THE full-term uterus is quite frequently dextrorotated; however, axial rotation through 180 degrees is exceedingly rare. The literature has recently been reviewed by Robinson and Du Vall,[1] Feinor and Kaldor,[2] and H. F. Day.[3] Adding my case to the list makes a total of 36 such cases reported. Of these, 29 cases had associated pathology or uterine anomalies that may account for their rotation, and in 7 cases, including mine, no apparent reason for the rotation could be noted. The case I am reporting is the only one, so far as I have been able to determine, which was entirely asymptomatic.

Mrs. W., aged 31, gravida i, para 0, was first seen on Dec. 21, 1937, stating that her last menstrual period began October 29, 1937. Her past history revealed that she had had an appendectomy and removal of the gall bladder in 1924, a suspension of the right kidney in 1925, and a dilatation and curettage with radium implantation for menorrhagia in 1926. Her menstrual periods began at 13 years of age, interval twenty-six days, duration four days, with slight dysmenorrhea.

Physical examination revealed a young woman, of fair complexion, height 5 feet 3 inches, weight 122. Head and neck negative, heart and lungs clear, high right rectus scar, well healed, with no tenderness, also a scar over the right kidney region. Pelvic examination showed the outlet marital, glands negative, support adequate, cervix posterior, uterus anterior, size of a six weeks' pregnancy and freely movable, no palpable adnexal masses, the diagonal conjugate was not reached, all bony pelvic
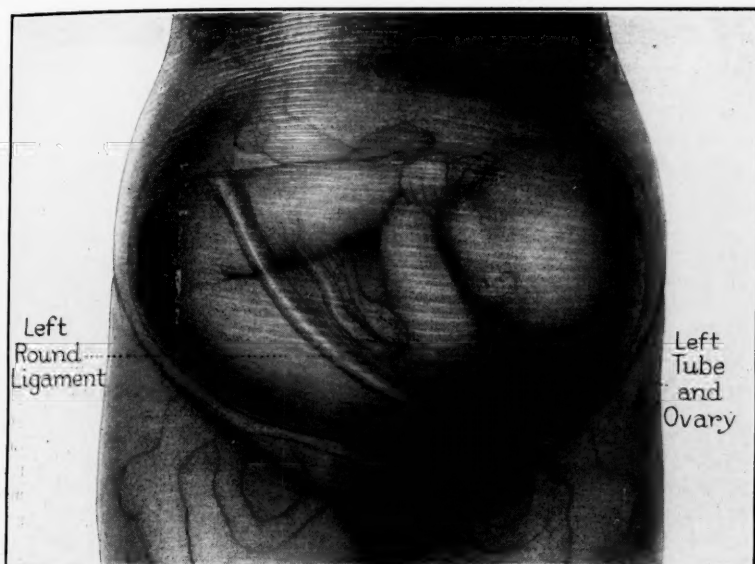
Fig. 1.—A drawing reconstructed from x-ray and surgery, illustrating a rotation of the uterus 180° to the right, with the fetus in transverse presentation.
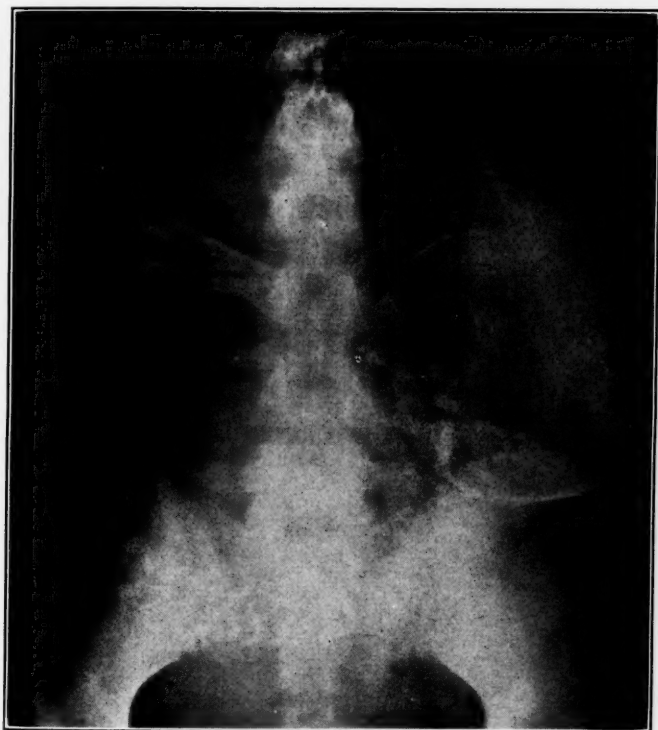


Fig 2.—Photograph of x-ray taken July 26, 1938.

findings were well within the range of normal. Joints and extremities normal, all reflexes active. Laboratory findings: Wassermann negative, hemoglobin 73 per cent, R.B.C. 4,910,000, urine negative for albumin and sugar.

Patient was seen at two-week intervals during the remainder of her pregnancy, during which time all findings were well within the range of normal. On July 5, 1938, a diagnosis of a transverse presentation was made. This was subsequently confirmed by an x-ray on July 26, 1938. Patient was subsequently seen at weekly intervals, and an elective cesarean section was decided upon for Aug. 7, 1938, which was approximately full term. Patient went into labor spontaneously on Aug. 5, 1938, at 10:00 A.M., was admitted to St. Vincents Hospital immediately. At the time of admission patient was having weak uterine contractions, and two hours later was operated upon under spinal anesthesia.

A low midline incision was made in order to enter the lower uterine segment. Upon opening the peritoneal cavity it was found that the uterus was rotated to the right 180 degrees, such that its posterior surface was presenting at the wound. The left round ligament was stretched diagonally across the uterus and measured about 2 cm. in diameter. The left broad ligament with tube and ovary was lying as shown in Fig. 1. Rather than attempt to deliver the fetus through a posterior incision it was decided to explore the upper abdomen, so the abdominal incision was lengthened to slightly above the umbilicus, thus enabling the hand to be introduced well over the fundus. The abdomen was entirely free of adhesions and the uterus seemed mobile such that with my hand up over the fundus I was able to rotate the uterus back to its normal position. A low classical operation was then done; a five-pound, nine-ounce fetus lying as a transverse presentation was found. A breech extraction was done on the fetus and the placenta and membranes extracted manually. A gauze pack was then put in the uterus with a shuttle through the cervix. The uterine wound was then closed in the usual manner. The uterus was then drawn up out of the abdomen and a thorough inspection made with no gross pathology or abnormalities noted. Abdomen was closed in the usual manner.

Her postoperative convalescence was uneventful. Mother and baby were discharged in good condition on the fourteenth postoperative day.

Follow-up examination on Sept. 6, 1938, showed the patient in good general condition, the uterus involuted, anterior, and freely movable, no palpable adnexal masses. Her subsequent course to date has been uneventful.

## DISCUSSION

In deciding upon an elective cesarean in this case it was felt that the transverse presentation of the fetus was caused by stenosis of the lower uterine segment, due probably to the use of radium for menorrhagia ten years previous. However, no evidence of stenosis could be found at operation. Whether the transverse presentation caused a rotation of the uterus or vice versa I am unable to state. Certainly this patient did not complain of pain such as might accompany a rotation of this type.

A case of this type raises one other very pertinent question, that is, the advisability of attempting a manual correction of transverse presentation. If this is attempted, the procedure should be cautious and gentle, with no undue force, and certainly the patient should not have anesthesia during the attempted conversion.

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# ANENCEPHALY IN A HUMAN EMBRYO TEN MILLIMETERS LONG

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THE embryo described here was obtained as the result of a spontaneous abortion from an unmarried woman 26 years old. She gave no history of amenorrhea and the possibility of pregnancy was denied. It was determined later that the father was about 65 years of age. The ovum was unruptured and measured 6 cm. in diameter. On opening the sac it was found to be filled with dark, greenish-colored amniotic fluid that had the consistency of bile. The quantity of fluid was excessive for the stage of development of the embryo. Since the clinical history of the patient was of no value in determining the age of the embryo, its size and developmental characteristics were used to estimate its approximate age.

On careful examination the embryo was found to be anencephalous. Its crown-rump length was 10 mm. What appeared to be an angiomatous mass was seen to extend from the occiput to the lumbar region. This mass covered a complete spina bifida. Anterior to the mass was a lighter colored structure which appeared to be part of the brain. This consisted of two anterior lobes and a triangular posterior part. These were probably atrophic cerebral hemispheres and midbrain, respectively. The left lobe was seen to be perforated when re-examined some months after first obtaining the specimen. The angiomatous-like mass appeared to be very fragile and a small portion had fallen away. The head was acutely dorsiflexed upon the shoulders, typical iniencephaly. The mouth was open and the tongue protruding. The eyes were situated well forward on the head. The nasal pits were discernible with the naked eye. On viewing the embryo anteriorly the parts referred to above as portions of the brain were seen to be flattened out. They extended downward in an overhanging manner and partially covered the frontal region. Laterally, these parts joined the so-called angiomatous mass where one might expect to find the developing ears. There was no evidence of these structures. The spine showed no convexity and no tail could be seen. The abdomen was prominent as in a normal embryo at this stage. There was no evidence of an umbilical hernia and the gut appeared to be within the abdomen.

The gross appearance of the sac was normal except for its size. It was comparatively large due to excessive amniotic fluid. Chorionic villi were present over the whole ovum. There appeared to be old blood clot adherent to the amnion.

Examination of the embryo under a dissecting microscope (×10) showed that the nasal pits had probably been formed recently. They were quite shallow. Facial fissures could not be defined with certainty, but there was a slight indication of a groove between the fused globular and maxillary processes. The only evidence of the developing ears was a pit on the right side just posterior to the mandibular arch. There were no tubercles seen and the hyoid arch was not defined. The branchial grooves could not be seen. The three segments of the forelimb could be recognized easily. The rudiments of the fingers were seen as very shallow indentations at the margins of the hands. The hindlimb also showed division into its main parts but the rudiments of the toes were not visible.

The absence of facial fissures and the presence of rudimentary fingers would suggest that the embryo was at the seven-weeks' stage of development. The absence of rudimentary toes and of an umbilical hernia indicate an earlier stage and its age was therefore estimated to be about 6.5 weeks.

The available literature on anencephaly and related malformations contains only one recent report of such a condition in an embryo, that of Dodds and DeAngelis (1937). They described an embryo of seven weeks and crown-rump measurement of 16.5 mm. which had a deformity of the head with complete absence of the brain. The upper portion of the head had a formation simulating a brain. This con-

sisted of highly vascular mesenchyme and had the form of cerebral hemispheres with prominent olfactory lobes and a cerebellum with two lobes. At the nape of the neck there was a flocculent mass protruding from a large opening which led downward into the spinal canal. They considered this mass to be broken down spinal cord. It was lost in preparation and was not sectioned. There was a wrinkled sheet of tissue loosely attached to the top of the head. They described this as typical of primitive nervous tissue having the characteristic appearance of the primitive neural tube with ependymal, mantle and marginal layers. Their conclusions were that the condition arose by failure of the neural tube to form from the neural plate in the cranial region at about the fourth week.

Attention is drawn to the flocculent mass described above by Dodds and De-Angelis. In its site it resembles the angiomatous mass seen in the specimen illustrated here.

Although no sections of the 10 mm. embryo have been made, the gross appearance of the mass at the nape of the neck is such as to leave little doubt that it consists of blood-filled tissue. Similar conditions are commonly seen in older specimens of anencephaly. It would seem only reasonable to assume that in this embryo the anencephaly resulted from an angiomatous growth in the tela chorioidea of the fourth ventricle. This results in a diminished blood supply to the brain and consequent atrophy. The condition must occur after the fourth week, because there is no apparent defect of the eyes. Against this postulation is the fact that new growths have never been demonstrated in fetuses. Mall's collection of embryos has been studied with care and two or three were seen to be somewhat similar to the one described here but no detailed account of their structure is given in his paper since he was concerned with the pathology of the membranes.

The reasons for not sectioning this embryo are: (1) The condition of the tissue is indefinite, the embryo may have been dead for some time before it was fixed, (2) it makes a valuable museum specimen as it is and sectioning may result in nothing.

## SUMMARY

1. An embryo 10 mm. long is described in detail and its age is estimated to be 6.5 weeks.

2. It shows definite anencephaly and is characterized by what appears to be an angiomatous mass at the occipital region.

3. Anencephaly is, in this case, probably caused by an angiomatous growth originating in the tela chorioidea of the fourth ventricle.

4. This specimen is one of a very small number in which anencephaly has been noted in an embryo.

I wish to express my thanks to Professor D. C. Matheson for his assistance.

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# ENTEROUTERINE FISTULAS

## William A. Dwyer, M.D., Paterson, N. J.

IN 1933 Danforth and Case[3] reviewed the recorded history of enterouterine fistulas and found 58 authentic cases. Kirchner[8] reported a case of sigmoidouterine fistulas. Since then, including cases not previously noted, 12 additional cases have been reported.

The following case of enterouterine fistula presents several interesting points. First, thirteen months after the onset of pregnancy, the fetus was finally extracted. Second, one cannot say with any degree of assurance that this was a traumatic rupture of the uterus following an attempt to empty the uterus, for there is a very strong possibility of its being a spontaneous rupture with a partial escape of the fetus into the abdominal cavity. This much we do know: the injury to the intestine was not instrumental but was caused by the skull bones perforating their way into the lumen of the gut.

The history of this case is that the patient became nauseated and was seized with excruciating pain in the epigastrium two hours after eating. The pain was so severe that the patient was unable to move. Her face was pale and her body covered with a cold sweat. At the time she was six months pregnant. The fundus uteri was at the level of the umbilicus. The cervix was closed. Her pregnancy up to this time was uneventful except for a complaint of right lower quadrant pain at two months. She had had her last regular monthly period on March 17, 1936 and had felt life just before the fifth month. With the onset of pain, however, fetal movement disappeared. For three days she complained of cramps in the hypogastrium and some vaginal bleeding. The external os, however, was closed, the cervix was soft and the fundus just below the umbilicus. The patient remained in bed three months. During this interval there was a constant brownish, foul-smelling vaginal discharge. Examination at the end of this period showed a fetal leg protruding through the cervix. Three days later the leg dropped out of the vagina. The following week there was occasional lower abdominal pain with a brownish vaginal discharge and several small fetal bones were expelled. The abdomen was soft and the fundus just below the level of the umbilicus. A month later (November 20) the discharge was less. The patient looked well, was out of bed. Her temperature and pulse were normal. The fundus was below the umbilicus, small and firm. The cervix was small, high up in the vaginal vault, closed. For the next two months she continued to pass bones per vaginam. Toward the end of that time, though the abdomen was soft, there was slight tenderness in the iliac fossae with a sense of a tender mass in the right lower quadrant.

On January 26, 1937 under a general anesthetic the cervix was dilated and 15 bones, including ribs and arm bones, were extracted. She was well for three weeks. Then she began to complain of pain in the left lower quadrant. This was followed by diarrhea lasting five days, toward the end of which she noticed bits of carrots and tomato skin in the vaginal discharge.

On April 9, 1937 the patient was admitted to the Gynecological Ward at St. Joseph's Hospital, complaining of foul-smelling vaginal discharge with a decided fecal odor and appearance, containing at times undigested food remnants and fetal bones. The vulva and labia were irritated.

Vaginal examination at the time showed the cervix high up in the right side of the vault, small and almost flush with the vault. It could not be brought down. The external os was open about 1/4 inch. Situated above the level of the internal os and apparently outside the uterus, anteriorly, was a small soft mass about 5 inches in diameter. The uterine cavity extended upward and to the right for a distance of six inches, and fetal bones could be distinctly felt with the sound. The fundus was fixed in position by an indurated mass that extended from the right side of the uterus to the right iliac fossa as far as the anterior superior spine.

Below this was a band extending to the mass in the front of the segment of the uterus. The left fornix was negative. Charcoal fed to the patient at this time appeared in the vagina the following morning.

On April 10 x-ray examination revealed a large shadow in the pelvis, which was stated to be a distended bladder rather than a fetal skull. Smaller shadows to the right of the fifth lumbar vertebra were suggestive of fetal bones.

The patient's pulse and temperature were normal on admission, Hb. 70 per cent; R. B. C. 4,320,000; W. B. C. 12,000; polymorphonuclears 74 per cent. Sedimentation time seventy minutes to the 18 mm. line. The urine and Wassermann reactions were negative.

At the time of operation the uterus was normal in size, drawn over to the right side of the pelvis, where it was fixed in position by a chronically inflamed tube and an inflammatory cyst attached to the side wall of the pelvis and extending in front of the uterus. There was a large mass in the right side, lower part of the abdomen, made up of adherent loops of small intestine and sigmoid and the remnants of a decomposed fetus. The skull bones which formed the upper limit of the mass had eroded into the lumen of the small intestine for a distance of about three inches, giving rise to an enterouterine fistula which opened into the posterior superior aspect of the fundus uteri. On separation of the adherent loops of small intestines and sigmoid, there was also found an opening into the large intestine 1 inch in diameter. The decomposed fetus consisted of skull bones, brain, part of the chest, and a few long bones. The left tube and ovary were normal in appearance.

After exploring the pelvis the mass in the lower part of the right side of the abdomen was opened, and the decomposed fetus was removed. Supravaginal hysterectomy and right salpingo-oophorectomy were done, with removal of a cyst on right side. The adherent loops of intestine were separated, 8 inches of ileum was resected and an end-to-end anastomosis done. The opening in the sigmoid was closed. Raw surfaces were peritonized. The wound was closed in layers, with drainage.

Her convalescence was not uneventful. There was a moderate amount of shock following the operation. On the third day she had a rather severe reaction following the injection of glucose. On the sixth day the wound showed evidence of infection. In a little over two weeks the infection was pretty well cleared up and she was doing nicely. A week later she was operated upon for an acute obstruction of the small intestine on the left side of the pelvis at about the junction of the distal portion of the jejunum with the ileum by a broad area of dense adhesions, apparently at the site of the previous fistulous opening in the sigmoid. The site of the anastomosis in the small intestine showed no evidence of obstruction. The obstruction was relieved and the patient returned to bed in good condition. Her subsequent course was uneventful and she is in excellent condition today.

### PATHOLOGIC FINDING (DR. I. G. GERBER)

One specimen consisted of a uterus, and right adnexa. The uterus was amputated supracervically and measured 5.0 cm. long. It was 5.0 cm. wide at the fundus and 3.5 cm. thick. The serous surface was covered with fibrous tags on all aspects. The left adnexa had been resected close to the tubal angle. On the right lateral border, just 1.0 cm. below the isthmus of the tube, there was an opening in the uterus, about 1.5 cm. in diameter. This could be probed directly into the endometrial cavity. The endometrial cavity was 4.0 cm. long and 3.0 cm. wide at the fundus. The myometrium was 1.6 cm. thick, and on section showed many scattered, small, pinhead-sized hemorrhagic foci. The endometrium was prominent, granular, and hemorrhagic with scattered superficial areas of grayish green appearance. The opening in the lateral uterine wall was covered by a similar gray green exudate, which extended about the orifice and onto the broad ligament and over the mesosalpinx, and along the mesial pole of the ovary. The tubo-ovarian ligament was shortened and thickened, and showed hemorrhagic discoloration. The ovary was 4.0 cm. in diameter, and cystic to the feel. On section it presented a large corpus luteum and adjacent to it several pea-sized, thin-walled cysts containing hemorrhagic thin fluid. The ovarian tissue was edematous. The tube was 11.5 cm. long and 1.2 cm. in average diameter. Its serosal surface was covered by fibrous tags.

The fimbriated extremity was patent and permitted ready probing along its entire length. The mucosa was pale gray and moist. Attached to the proximal aspect of the tube there was a flap of peritoneum measuring 4.0 by 4.0 cm.

A second specimen consisted of a number of fetal bones. These represented skull bones, and short and long bones of the extremities. The bones were covered by a dirty grayish exudate, and were soft. Some were granular and friable.

A third specimen consisted of a portion of small intestine, which was 18.0 cm. long. On its serosal aspect there were a number of fibrous tags. There was a central defect in the intestine which was 9.0 cm. long. At the site of the defect the edges were ragged, ulcerated and piled up. The ulceration was about 5.0 cm. wide and almost completely encircled the bowel lumen. There was a small amount of mesentery attached which was discolored and thickened. Upon opening the intestine the wall was found to be markedly thickened. The mucosa at the site of the defect was hemorrhagic and ulcerated. Proximal and distal to the ulcerated area the mucosa was intact, and somewhat edematous.
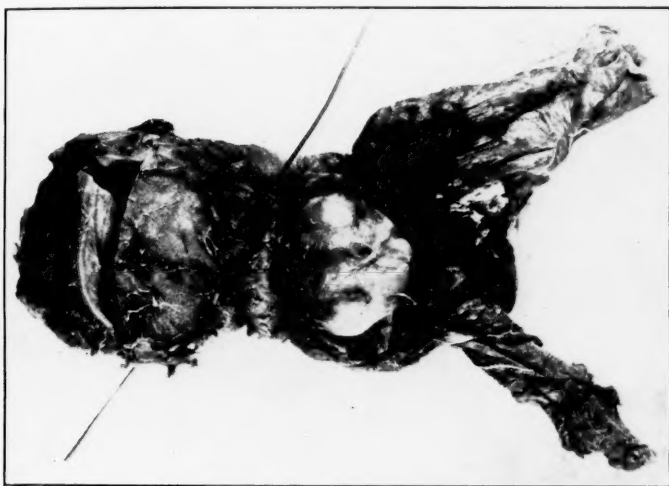


Fig. 1.—Uterus and right adnexa. Probe shows communication between endometrial cavity and abscess in broad ligament from which site remnants of fetus were removed.

*Microscopic Examination.*—The bones were not examined. Sections of the uterus showed a replacement of the endometrium by a broad layer of fibrin and inflammatory cells consisting chiefly of polymorphonuclear leucocytes and lymphocytes. The inflammatory reaction extended into the myometrium at several points. Where residual endometrial glands were present, these were small and collapsed and their surface covered by masses of fibrin. Other sections, taken near to site of perforation, showed areas of decidual reaction of the endometrium in which no glands were seen, and scattered areas in which there were syncytial giant cells. Chorionic villi were not noted. Sections of the tube and ovary showed chiefly adventitial inflammatory reaction with edema. Examination of the intestine revealed an extensive inflammatory reaction involving all coats, with marked edema and hemorrhage. There was complete necrosis of the mucosa with replacement fibrosis of the muscularis, and the serosa was covered by a layer of fibrin and polymorphonuclear leucocytes. There were scattered calcific foci in the subserosa with foreign body giant cell reaction and many pigmented macrophages.

*Diagnosis.*—Supracervically amputated uterus showing acute purulent endometritis and subacute myometritis, with decidual reaction and syncytial giant cells. Acute necrotizing enteritis. Perisalpingitis and peri-oophoritis. Corpus luteum and follicular cysts of the ovary. Perforation of the right lateral uterine wall, with localized abscess. Fetal bones.

*Note:* The presence of focal decidual reaction together with syncytial giant cells in the uterus speaks for a probably intrauterine pregnancy.

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99 Park Avenue

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# SIGMOIDAL CUTANEOUS (FECAL) FISTULA

S. N. Mendelsohn, M.D., Cincinnati, O.

*(From the Department of Surgery, The Jewish Hospital)*

THIS case is presented in view of the unusual type of accident caused by an abortionist, and because it demonstrates that iodized oil may be a valuable therapeutic agent in some types of large bowel fistula communicating with the skin.

Mrs. C. O. S., a 47-year-old, native white woman, was first seen June 17, 1937, at her home with complaints of lower abdominal and pelvic pain. The patient appeared subacutely ill. The history revealed similar attacks ''many years ago,'' with the present illness extending back for some two weeks. There had been a discharge of mucopurulent character associated with the menses. The temperature was 101° F., pulse 96. The past history did not reveal any illnesses of importance. The family history was not relevant. There were two adult children, living and well. Both pregnancies had been normal and uneventful, and she denied ever having any uterine manipulation. The menses were regular, every twenty-eight to thirty days, lasting from four to five days, and of average flow. There was a moderate dysmenorrhea with some exacerbation recently. Abdominal examination disclosed marked tenderness throughout the entire lower abdomen, with diffuse muscle spasm. Vaginal examination revealed an extremely tender mass the size of a large orange in the left adnexal region. The sedimentation rate was rapid, falling 18 mm. in twelve minutes.

A diagnosis of an acute left tubo-ovarian abscess was made and treatment carried out at home. Subsequently, the sedimentation rate, which had been persistently rapid, gradually returned to within normal limits, and the mass became partially resorbed. Eight weeks after initial examination, the left sided mass was approximately one-half its original size and the sedimentation rate was consistently within normal limits. At this time operation was recommended and the patient was admitted to the hospital on Oct. 17, 1937. The red blood count was 4,130,000, the white count 12,050, and the hemoglobin 70 per cent (Dare). A blood Wassermann test was negative. The urinalysis revealed numerous pus cells, but was otherwise not significant.

At laparotomy a great number of adhesions were found, with the omentum plastered down to the bladder and the uterus, both anteriorly and posteriorly. Some loops of small bowel were adherent to the posterior aspect of the uterus. These adhesions were freed. There was a cordlike structure extending from the sigmoid at the rectosigmoid junction to the fundus of the uterus at its midpoint. This was cut upon in the belief that we were dealing with an unusually thick fibrous band. It was found to contain a rubber catheter with both ends cut upon a sharp bias,
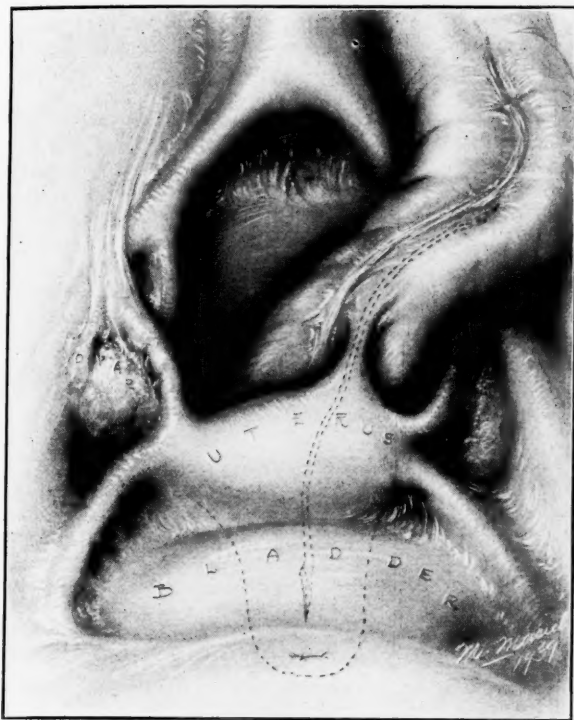
Fig. 1.—The catheter is seen piercing the posterior uterine wall and its distal portion lying within the sigmoid.
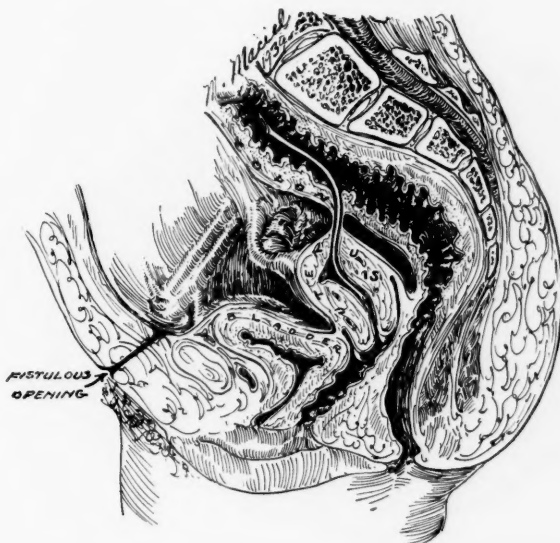


Fig. 2.—The fistulous opening is seen suprapubically.  The catheter shown had been removed at operation.

and measuring 31 cm. in length. Approximately half of this rubber tube was found lying in the uterine cavity, piercing the fundal wall, and traversing the cordlike structure. The distal half of the tube was in the sigmoid directed toward the splenic flexure of the colon (Fig. 1). The catheter was removed and the sigmoidal and uterine openings were closed by fine catgut sutures. Two drains of soft rubber were inserted to the sutured sigmoid colon and brought out through the lower angle of the abdominal wound. The cordlike structure, through which the catheter traversed to the sigmoid, was removed and reported histologically as ''a mass of chronic inflammatory fibrous tissue partially infiltrated by a subacute and acute inflammatory exudate of granulation tissue.''

The soft rubber drainage tubes were totally removed by the fifth day after operation. The immediate postoperative course was uneventful and the patient was dismissed in two weeks. At this time there was a small amount of serosanguineous material at the drainage site. Approximately one month later the character of this discharge had become definitely fecal in appearance and odor (Fig. 2). Methylene blue injected into the abdominocutaneous opening appeared quickly at the anus. The amount was small but the drainage persisted for more than four months.

More than four months after operation the sigmoidal cutaneous fistula was still discharging despite all attempts at conservative treatment. The patient, therefore, was treated by means of the introduction of iodized poppy seed oil (lipiodol) into the fistulous tract (Mendelsohn and Schriver).[1] The intestinal contents were evacuated by means of small irrigations; a nonresidue or liquid diet was administered, and salines were used to help empty the entire gastroenteric tract.

Four to 10 c.c. of lipiodol were slowly injected into the tract through a small soft catheter which had been previously passed through the cutaneous opening and the tube then gently removed. A plug of gauze was then placed over the mouth of the opening. This was repeated at four- to five-day intervals, and at the end of approximately three weeks the tract had completely closed.

REFERENCE

(1) *Mendelsohn, S. N., and Schriver, L. H.:*  Surgery 4: 430, 1938.

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**McCullagh, E. Perry, and Cuyler, W. Kenneth:  The Friedman Test and Pituitary Tumor,** Endocrinology 21: 8, 1937.

Positive Friedman test results have been observed in 8 of 15 cases of pituitary tumor. The 7 cases in which negative Friedman test results were obtained are described briefly. The diagnosis of tumor was verified at operation or autopsy in 4 instances and histologic descriptions are available in 3; one was an acidophilic adenoma, one a basophilic adenoma, and the other a cystic adenoma which contained large numbers of both acidophilic and basophilic cells.

Of the 8 cases in which positive reactions were obtained, the presence of tumor was verified at operation or autopsy in 4 instances. Two were basophilic adenomas, one of which was found in a patient with the syndrome of pituitary basophilism; one was an acidophilic adenoma, and one a papillary carcinoma of Rathke's pouch involving the pituitary. Of the unverified tumors, 3 occurred in patients with acromegaly and therefore these tumors were probably acidophilic adenomas; a fourth was associated with signs of hypogonadism.

In cases of pituitary tumor in which the Friedman test reaction is positive, radiation therapy to the pituitary may be followed by marked diminution in the excretion of prolan as judged by this test; in two instances, this has been accompanied by a diminution in the excretion of testicular hormone.

J. Thornwell Witherspoon

# Department of Maternal Welfare

CONDUCTED BY FRED L. ADAIR, M.D., CHICAGO, ILL.

## A REPORT ON THE PROGRAM OF THE NORTH DAKOTA COMMITTEE ON MATERNAL WELFARE AND CHILD HEALTH FOR 1938

JOHN H. MOORE, M.D., F.A.C.S., CHAIRMAN, GRAND FORKS, N. DAK.

THE North Dakota Committee on Maternal Welfare and Child Health has been occupied during 1938 with three major objectives in its plan to further maternal and child welfare throughout the state. At its final meeting for the year, held in Grand Forks, N. Dak., on Dec. 17, 1938, the entire personnel of the committee, consisting of Dr. J. F. Hanna and Dr. Ralph E. Pray of Fargo, Dr. J. L. Conrad, Jamestown, Dr. Paul W. Freise, Bismarck, Dr. E. M. Ransom, Minot, Dr. M. D. Westley, Cooperstown, Dr. John D. Graham, Devils Lake, Dr. Philip H. Woutat, Grand Forks, Dr. Maysil M. Williams of Bismarck, State Health Officer and Secretary of the Committee, and the Chairman, Dr. John H. Moore of Grand Forks, was in attendance.

The presence of Dr. August C. Orr and Dr. Elizabeth Smith of the Department of Maternal Welfare and Child Hygiene of the North Dakota State Department of Health was made possible by Dr. Maysil M. Williams who, in her dual role of State Health Officer and Secretary of the Committee, has continued the policy of cooperation with the Committee.

The first major objective for the year was a continuation of the Educational Program for Physicians. A subcommittee consisting of Dr. Ralph E. Pray and Dr. J. L. Conrad secured Dr. William F. Mengert, Associate Professor of Obstetrics and Gynecology at the University of Iowa, and Dr. W. H. Thompson, Assistant Professor of Pediatrics at the University of Minnesota, to give this year's course in Obstetrics and Pediatrics. Approximately 300 physicians attended the combined courses given in five cities during October, 1938. Late afternoon and evening sessions were held in each city visited for two successive weeks, a day in each city. That this plan was popular was evident by the replies to a questionnaire sent to the physicians upon the termination of the course. The majority favored continuing this plan another year and October was favored as the month in which to hold the courses. Many facts of interest were revealed by the questionnaire, and these will be used by the subcommittee in its plan for the courses in 1939.

At the conclusion of the course the booklet *Maternal Care*, approved by The American Committee on Maternal Welfare, Inc., was sent to physicians by the State Department of Health with the endorsement of the North Dakota Committee.

The Committee has authorized its subcommittee on the Educational Program for Physicians to enlarge its work for 1939, and it is hoped that more intensive postgraduate education will be made available to physicians thereby. It is certain that this type of instruction is very popular among North Dakota physicians.

The second major objective of the Committee for 1938 was an individual analysis of all maternal deaths occurring in North Dakota. The study was started for the year 1937 by the State Department of Health, Division of Child Hygiene, at the request of the North Dakota State Committee on Maternal Welfare and Child Health. While North Dakota has a low maternal mortality, it was felt that an individual analysis of all maternal deaths and a ''break-down'' of all the

facts presented might prove valuable in effecting a further reduction. This study included all deaths in which pregnancy or childbirth was mentioned by the physician who registered the death and also the deaths of women who were between the ages of 15 and 49 years and who were shown by birth certificates to have been delivered of a live or stillborn infant within three months prior to death. The registrar of the Bureau of Vital Statistics copied death certificates of all cases in which the puerperal state was mentioned and the physicians who signed these certificates were interviewed personally by physicians from the State Department of Health. All physicians were willing to cooperate and expressed approval of the survey as it was being made. This report will be presented elsewhere as the first of a series of annual reports by the Committee. The survey for 1938 is well under way.

The third and final objective of the Committee for 1938 was the launching of a program designed to reduce the incidence of neonatal mortality. According to the Director of the Division of Child Hygiene of the State Department of Health, approximately 30 to 40 per cent of the neonatal deaths in North Dakota are due to prematurity. The Committee has adopted the following plan:

1. The establishment of recognized methods of management and feeding of the premature infant.

2. The purchase and distribution of low cost incubators to North Dakota hospitals and the eventual placement of incubators in other key spots in the state where facilities are widely spaced.

3. The adoption of a modern, recognized technique of resuscitation of premature and newborn infants in all hospitals.

4. The establishment of a standard summary record form, such as that designed by Dr. R. G. Moe of Duluth, in all hospitals so that statistical data can readily be collected.

5. The carrying out of an educational program of seminars to be conducted by pediatricians selected by the Committee.

6. The securing of statistical data on the causes of neonatal deaths both in hospital and in home deliveries.

7. The publication of a preliminary report of this plan as information becomes available and as conditions warrant.

The Committee feels that these objectives have the support of the physicians. Without this support this or any other program looking toward a reduction of maternal and infant mortality would fail. The members of the Committee are private practitioners who know conditions in the rural and small urban communities in this state. Working with a State Health Department that knows the problems and has the viewpoint of the private practitioner of medicine, it hopes to make effective the all-important patient-private physician relationship, the back-bone of medical practice in general and particularly in the fields of obstetrics and pediatrics.

# Society Transactions

## CHICAGO GYNECOLOGICAL SOCIETY

### MEETING OF DECEMBER 16, 1938

The following papers and case reports were presented:

**Case of Krukenberg Tumor.** Dr. W. C. Danforth.

**A Case of Spontaneous Abortion Through Posterior Wall of the Cervix.** Dr. M. J. Kiley.

**A Preliminary Report on the Use of Sulfanilamide in Puerperal and Post-abortal Infections.** Dr. T. J. Morris. (For original article, see page 67.)

**Use of a Sulfanilamide Derivative in the Treatment of Gonorrhea in Pregnant and Nonpregnant Women.** Drs. E. J. Bomze, P. G. Fuerstner and F. H. Falls. (For original article, see page 73.)

**The Excretion of Free and Acetylsulfanilamide in Human Breast Milk.** Drs. L. R. Hac, F. L. Adair and H. C. Hesseltine. (For original article, see page 57.)

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**Salatich, P. B.: Varicose Veins of the Broad Ligament and Their Consequences,** South. M. J. 31: 697, 1938.

The failure of various operative procedures for the correction of uterine displacement to alleviate backache, menstrual disturbances and other associated symptoms suggested that possibly additional unrecognized factors might exist. From pre- and postoperative examinations it was observed that those women whose symptoms were most marked and persisted following round ligament shortening and suspension procedures had variable degrees of enlargement of the veins of the broad ligament.

The most distressing symptom associated with this condition is pain which characteristically is influenced by posture, being aggravated by standing. Various menstrual disturbances may occur, especially in younger patients; these develop upon a basis of ovarian congestion. A watery leucorrhea is common.

If, on pelvic examination there is no palpatory evidence of tubal or ovarian enlargement or pain, dilated veins should be considered as a possible etiologic factor. If they are present considerable pain will be caused by pressing upward in the parametrium with the fingers at the sides of the cervix in line with the axis of the uterus. Some softening of the cervix is noted, and the uterus though boggy need not be retroverted.

Conservative operation is recommended for the relief of the condition. The procedure includes vein ligation, especially the ovarians, plication of the uterosacral ligaments to relieve congestion in the more deeply situated veins about the uterine artery, and round ligament shortening.

Radium should not be used to check menorrhagia, because there is danger of rupture of the thin-walled tortuous veins; the backache remains unrelieved.

<div align="right">Arnold Goldberger</div>

# Department of Reviews and Abstracts

## Selected Abstracts

### The Newborn Infant

**Donaldson, S. W.: A Study of the Relation Between Birth Weight and Size of the Thymus Shadow in 2,000 Newborn,** Ohio State M. J. **34:** 538, 1938.

Of 2,000 newborn infants 18.4 per cent showed roentgenologically some degree of enlargement of the thymus, and 11.15 per cent were classified as definitely enlarged. The percentage of enlargement in the heavier babies is higher in the male. The heaviest baby in both groups was negative for thymic enlargement. The uniformity of the percentage of enlargement in the normal weight babies with a gradual increase as birth weight increases would imply that the size of the thymic shadow was proportionate to birth weight rather than that the gland was pathologically enlarged.

No ill effects were noted from small doses of radiation administered as a prophylactic measure. Not enough evidence was presented in this series to indicate that only those babies weighing more than 8½ pounds should be examined for an abnormal thymus shadow. Therapy was administered merely upon roentgen ray evidence of enlargement. Decrease in the size of the thymus shadow was noted in all patients treated and re-examined. No thymic death has occurred in any child in this study as far as the author's present records are concerned.

J. P. GREENHILL.

**Kaern, T.: The Birth of Abnormally Large Children,** Acta obst. et. gynec. Scandinav. **16:** 189, 1936.

The author analyzed a series of 228 children who weighed more than 4,500 gm. at birth. In the Copenhagen clinic the incidence of these children was 0.9 per cent. Among the etiologic factors accounting for these large children the author mentions the sex of the child, the mother's age, her height and weight, and previous births. The incidence of operative intervention was 19.3 per cent. The shoulders gave particular difficulty during delivery. Hemorrhages of more than 500 c.c. occurred in 24.1 per cent of these cases in comparison with the usual incidence of 4.9 per cent in the author's clinic. The death rate among the large children was 14.9 per cent as against 3.2 per cent for all the newborn. The author believes that labor should be induced before term when children have reached a normal birth weight.

J. P. GREENHILL.

**Holtz, S.: The Causes of Premature Labor and the Prognosis of Babies Born Before Term,** Gynécologie **35:** 65, 1936

In a series of over 60,000 labor cases the author found that 313 babies were born before term (5.1 per cent). Premature labors were not found to occur more frequently in primiparas than in multiparas. The age of the mother was not a factor. However, abnormal presentation such as breech occurs much more frequently among premature babies than among those at full term. Thirty-nine of the babies died before term and 18 died during labor. Most of the children were born alive and subsequently died of debility. The author comes to the conclusion that the prognosis of babies born before term is very bad. Of the babies weighing less than 2,000 gm. 21 per cent died before labor, 8 per cent during

delivery, and 40 per cent after birth, whereas, of the babies weighing more than 2,000 gm., 4 per cent died before labor, 3 per cent died during labor and 10 per cent after birth. Thus of babies weighing less than 2,000 gm., only 31 per cent survived, but of those above 2,000 gm., 83 per cent survived.

<div align="right">J. P. GREENHILL.</div>

**Bruecke, Hans: The Problem of Injecting Medication Into the Child During Birth,** München. med. Wchnschr. 83: 2096, 1936.

Bruecke enters into a discussion on the merits and demerits concerning the use of cardiozol during labor for the improvement of fetal cardiac action.

His observations were as follows: Before the use of cardiozol, in 5,864 births, the total of fetal fatalities was 210 (3.60 per cent); after employment of cardiozol, in 9,263 births, the total fatalities were 301 (3.24 per cent). With this difference of only 0.36 per cent, he does not feel that a value of cardiozol has become apparent.

<div align="right">C. E. PROSHEK.</div>

**Cole, W. C. C.: Obstetrical Influences on the Weight Curve of the Newborn,** Surg. Gynec. Obst. 68: 179, 1939.

The conception that the ''normal'' newborn infant may be in a state of mild shock is relatively new. If this proves to be correct, such shock should greatly modify not only our routine care of newborn babies but many obstetric procedures.

A statistical analysis of 996 newborn babies is presented with the view of determining whether obstetric and neonatal procedures influence weight loss in the newborn. It is shown that certain factors tend definitely to increase the loss in weight and that others tend to decrease the loss. It seems conclusive that the weight loss of the newborn is not entirely physiologic. The evidence presented seems to confirm the idea that the ''normal'' newborn is in a state of mild shock as a result of the trauma of labor. In general, factors which tend to retard or ease the second stage of labor appear to be favorable to the child.

<div align="right">WILLIAM C. HENSKE.</div>

**Clifford, Stewart H., and Irving, Frederick C.: Analgesia, Anesthesia and the Newborn Infant,** Surg. Gynec. Obst. 65: 23, 1937.

Opium derivatives administered during labor have been found to exert an unfavorable influence upon the condition of the newborn infant proportional to the amount given and to the time interval between the administration of the drug and the birth of the child. In this group 57 per cent of the infants required some stimulation before they would breathe and cry normally, and 23 per cent were asphyxiated to the point of requiring artificial resuscitation. Successful maternal amnesia was obtained in but 34 per cent of the cases.

The barbiturates have had no harmful effect either upon the life of the fetus or upon the life of the newborn infant. Over 10,000 mothers have received sodium amytal or pentobarbital in the past five years, and during this interval both the stillbirths and the newborn infant death rates have fallen below the level of the preceding five years. Following analgesia through a combination of barbiturate, scopolamine, rectal ether, nitrous oxide-oxygen and small amounts of ether, 37 per cent of the infants required some stimulation before normal respirations were established, while 31 per cent were sufficiently asphyxiated to require artificial resuscitation. Complete amnesia was obtained for 78 per cent of the mothers of this group.

Neither pentobarbital, sodium amytal, scopolamine, rectal ether, nor paraldehyde could be held responsible for the symptoms of asphyxia that were encountered in some of the newborn infants. It is the writers' belief that the untoward effects of analgesia may well be explained by nitrous oxide-oxygen mixtures above the 85:15 level, producing a degree of fetal asphyxia dependent upon the duration of the exposure and the size of the infant.

<div align="right">WILLIAM C. HENSKE.</div>

**Erbsloeh, Joachim:  The Clinical Significance of Skull Fractures of the Newborn,** Arch. f. Gynäk. **165**: 73, 1937.

Skull fractures of the newborn can and do result from spontaneous as well as from instrumental deliveries.  Such trauma need not be fatal, in fact usually is not.  Fatalities and sequelae are usually the results of intracranial hemorrhage and rarely of simple skull fracture.  In fact, recovery is complete and uneventful unless there is a resulting hemorrhage somewhere in the central nervous system. Uncomplicated skull fractures are usually symptomless, require no therapy and leave no traces which can be determined roentgenologically.  Uncomplicated skull fractures are therefore probably much more common than is generally supposed. The only known complication of simple skull fracture is the ''meningocele spuria traumatica.''

RALPH A. REIS.

**Küstner, H.:  Intracranial Injury of Children During Labor,** Med. Klin. **33**: 221, 1937.

Among 7,319 children born in the Leipzig clinic, 453 (6.2 per cent) were born dead or died during the first week.  However, of the 5,958 children born spontaneously, only 228 (3.8 per cent) were born dead or died.  Of these 228 children, 47 died during labor, were immature or monsters and hence could not have been saved under any conditions.  In addition 27 babies died of asphyxia and 14 showed definite cranial trauma.  Out of the total of 228 babies, 129 died not during labor but during the first week of life and most of these (76 per cent) perished during the first 2 days.  Of these 129 children, however, 104 (80 per cent) were premature. Hence the neonatal death rate of spontaneously born children can be reduced only by preventing premature labor.

The situation is entirely different in the case of operative deliveries.  Among the 7,319 children in this series, 1,356 were delivered by operative means and of these, 220 (16.2 per cent) died.  Among these 1,356 babies, 1,225 were full term and only 131 were premature.  Among the 1,225 full term babies 10.3 per cent were born dead and among the 131 prematures 71.8 per cent died.  Some of these children died as the result of illness of the mother.

The author's study leads him to believe that fear of cerebral damage to the newborn during labor is not justified.  While it is true that a certain proportion of babies die as a result of such injury, most babies die as the result of other complications which endanger the mother far more.  Babies born with cerebral injury should not be treated because while a few recover, most show physical and mental disturbances later in life.

J. P. GREENHILL.

**Brauder, T.:  Intracranial Birth Injuries in Breech Deliveries,** Monatschr. f. Geburtsh. u. Gynäk. **105**: 205, 1937.

From a study of his own cases and from a review of the literature, Brauder comes to the conclusion that the death rate in breech deliveries is higher in cases where manual aid is used than in cases where the delivery is spontaneous. Likewise the fetal mortality is higher in cases where extraction is resorted to than in cases of manual aid.  Autopsies on newborn babies with intracranial hemorrhage show an unusually high incidence of babies born by the breech.  The danger in breech deliveries is particularly great in premature babies.  Evidences of intracranial hemorrhage are not infrequently observed in babies born breech first and in later life these babies develop epilepsy, spastic paralysis, and imbecility.  Among the author's mentally defective twins, the incidence of breech deliveries was very high.  One cause for the increased incidence of intracranial bleeding in breech cases is the very rapid delivery of the head through the pelvic canal.  The same applies to babies delivered by high forceps and in precipitate labors.  Since mental deficiency is so frequent in breech cases and since breech presentations occur in 3 per cent of all labors, prophylactically a breech presentation should often be an indication for cesarean section.

J. P. GREENHILL.

**Fischer, Eberhard:** **Later Development of Children Suffering From Birth Trauma Spasms,** München. Med. Wchnschr. 85: 1582, 1938.

Follow-up examinations of 18 children afflicted with birth trauma spasms revealed the following results:

Eight children had developed normally, physically and mentally, save for insignificant defects. The family history showed no peculiarities.

Out of five children who died, the cause of death in four cases was a disease of the central nervous system together with spasms which had prevailed ever since birth. It may be assumed, therefore, that the children died as a result of the birth trauma. In the case of one child who died after a vaccination for smallpox it could not be determined whether the previous birth trauma had caused a lowered resistance and thus indirectly had caused death. As to one of these five children, a heredity of the same ailment in the family group could be found and in another case the heredity was questionable.

In the cases of five children with permanent defects, there could be found, besides other disturbances, various degrees of feeble mindedness. The connection of birth trauma and permanent defect was made evident by the continuation of pathologic symptoms. Localized symptoms which permitted of a localization of the brain injury were present in all cases more or less distinctly (Jacksonian epilepsy, speech defects, difficulty of hearing). Thus the brain injury may have caused the permanent defect. Investigations of the family histories have not shown in all cases a heredity for a similar ailment, but a strong predisposition for nervous and mental disturbances could be clearly shown in all cases. Thus it is possible that the pathologic heredity might be the cause of these disturbances. The nervous and mental disturbances of these children could not be attributed to the exogenous factor, the birth trauma, or the endogenous factor, the heredity, alone, as both factors in most cases operate concurrently. How far the factors might influence each other, cannot be determined.

The high number of sick and dead children in comparison to the low number of healthy ones seems to prove that in this investigation one was dealing with severe and definite cases of intracranial hemorrhage so that subsequent disturbances were to be expected in greater numbers.

From the manner of delivery and the clinical symptomatology of the intracranial hemorrhage post partum, no prognosis for the further development could be made.

All the newborns afflicted with intracranial hemorrhage were treated in the same conservative manner, so that the method of treatment could not have caused any difference in the development of the children.

C. E. PROSHEK.

**Gordon, G. C.:** **Persistent Overmoulding of the Skull Bones Causing Fits in an Infant,** Brit. M. J. 1: 14, 1938.

The case of an infant having convulsive seizures is reported. One older child was born three and one-half years before and is healthy and normal. This child was born spontaneously after less than one hour of labor. The first convulsions occurred on the fourteenth day. They continued intermittently until the thirty-fifth day. At three months of age, the time when the case was reported, no more fits had occurred. Examination at the time of the first seizure revealed an overlapping of the skull bones at the suture lines and an obliteration of both fontanels. The baby was also blind. Because there was no evidence of paresis, no cutaneous sensory loss, a severe degree of vomiting and a blindness, the author feels that the cause was a generalized increased intracranial pressure from the overmolding of the skull bones rather than from an intracranial hemorrhage. At three months of age, the bones overlapped not any longer, the anterior fontanel was 0.5 inch in diameter, the degree of blindness was decreasing, and the child was apparently recovering.

F. L. ADAIR AND J. A. HAUGEN.

**Philipps, S.: Hemorrhage and Rupture of the Adrenal in the Newborn Infant,** South. M. J. **31:** 759, 1938.

Adrenal hemorrhage in the newborn is a fairly common occurrence, but it is usually discovered only at post-mortem examination. Mention is made of the occurrence of bilateral adrenal hemorrhage in an infant who presented clinical signs suggestive of cerebral hemorrhage which was not verified at necropsy.

The author reports a case of an apparently normal male infant weighing nine pounds at the time of its spontaneous birth. On the fourth day the baby appeared acutely ill. It was lethargic, feverish, had convulsive twitches, and in the right hypochondrium a lemon-sized mass was palpable. In twenty-four hours the hemoglobin fell from 75 per cent to 45 per cent. The child died on the fifth day.

The abdomen was found filled with blood which had infiltrated retroperitoneally, and had forced its way through the diaphragmatic hiatuses into the thoracic cavity. The right adrenal was torn and largely destroyed by hemorrhage into its substance.

The author believes that the salient clinical features in this patient were shock and symptoms of exsanguination. He doubts whether the use of a potent cortical hormone extract in accordance with Goldzieher's hypothesis of acute adrenal insufficiency would have been of value.

ARNOLD GOLDBERGER.

**Fournier, R., and Klein, R.: Twin Pregnancies With Death of One Baby,** Bull. Soc. d'obst. et de gynée. **26:** 350, 1937.

In a series of 20,000 labors the authors found 210 sets of twins. Among the latter, one child was born dead in 13 instances or in 6 per cent of the twins. Among these 13 cases, syphilis was definitely present three times; syphilis was most likely present in six additional cases; one mother had toxemia and in two cases there were numerous infarcts in the placentas. Hence, syphilis caused the death of most of these fetuses.

J. P. GREENHILL.

**Randall, Lawrence M., and Rynearson, Edward H.: Delivery and Care of the New-Born Infant of the Diabetic Mother,** J. A. M. A. **107:** 919, 1937.

The mortality among infants born to diabetic mothers has continued high in spite of advanced knowledge in the treatment of diabetes. By subjecting seven successive diabetic mothers to cesarean section between the thirty-third and thirty-seventh weeks of pregnancy, the authors feel they have avoided those dangers which arise during the last few weeks of pregnancy and have saved the mother and child from the risk of a difficult labor. All infants were born alive. The concentration of sugar in the blood of the mother, the infant and the umbilical cord were determined immediately after delivery. Hypoglycemia of the newborn was observed in a few cases and seems to support the view that the child's pancreas continues to overfunction. Whenever twitchings, convulsive movements or cyanosis indicate the development of hypoglycemia, 10 c.c. of a 10 per cent solution of dextrose is given by mouth if possible; otherwise it is administered intramuscularly. The length of the period of danger from hypoglycemia cannot be predicted with accuracy.

GROVER LIESE.

**Whitaker: Anemia and Jaundice in the New-Born,** Illinois M. J. **74:** 134, 1938.

The fetus really exists in a state of oxygen want or relative anoxemia. Pure oxygenated blood exists in only one vessel of the fetal circulation, the umbilical vein, coming from the placenta to the fetus. Nature produces an increased amount of red blood cells in response to the relative anoxemia.

It is apparent then that the infant enters this world with a polycythemia, usually showing red cells from 5 to 7 million at birth with correspondingly elevated

hemoglobin values. This high count tends to persist during the first week and then slowly falls. There is no need for the increased red cells after birth; they are destroyed and the hemoglobin liberated is broken down into bilirubin, the iron free pigment, and hemosiderin, the iron-containing pigment. The bilirubin value rises, and when it reaches a certain point, visible jaundice results.

Physiologic jaundice, normally in a mild form, appears about the third day or later and tends to clear up in a few days. No bile is noted in the urine. Whenever the clinician has ruled out the ordinary type of physiologic jaundice in the newborn, whatever the cause for the case at hand, the prognosis is serious. Various studies show mortality rates up to 80 per cent. This form may occur sporadically, but is usually familial. It is practically always evident before the third day. The icterus is intense, the infant appears gravely ill, being quite drowsy and usually prostated. Death may occur quickly. The liver and spleen are enlarged. There is bile in the stools and also in the urine. These cases rarely recover spontaneously. There is usually an associated anemia, the outward signs of which are masked by the intense jaundice, but anemia is not a necessary accompaniment. Extensive hemorrhages may occur from the mucous membranes or into the skin.

Examination of the blood in infants with this type of jaundice is exceedingly important and yields findings almost pathognomonic. The presence of nucleated red blood cells in abnormal numbers is the classical finding. Nucleated red cells should not appear in the peripheral blood of the normal infant after the first week. In these cases, however, one usually finds an increase in immature red cell forms, megaloblasts, erythroblasts, normoblasts and reticulocytes. The characteristic cell is a macrocyte, indicating that the mean diameter of the red cells is increased in icterus gravis. The van den Bergh tests in these cases show a markedly increased indirect reaction, and also a direct immediate reaction, really a biphasic response which implies necrosis of the liver cells.

The pathology noted in cases of icterus gravis consists primarily of a generalized yellowish tint of the various organs and serous surfaces with the essential findings being noted in the liver, spleen, kidneys, and consisting of islands of extramedullary blood formation.

Treatment to date for icterus gravis with or without erythroblastosis consists chiefly in early blood transfusions or the use of maternal serum.

J. P. GREENHILL.

# Items

## American Board of Obstetrics and Gynecology

At the recent examinations held by the Board at St. Louis, Missouri, on May 13, 14, 15, and 16, 228 candidates were certified by the Board.

At the annual meeting of the Board, held in St. Louis on May 12, 1939, it was found necessary, on account of increased administration expenses, to increase the application and examination fees. Effective immediately, these are to be as follows: Application fee $15.00, payable upon submission of application for review by Board. Examination fee $75.00, payable upon notification to candidate of acceptance of the application and assignment for examination. Neither fee is returnable. This increase does not apply to candidates whose applications were filed prior to May 12, 1939.

The next written examination and review of case histories (Part I) for Group B candidates will be held in various cities of the United States and Canada on Saturday, December 2, 1939, at 2:00 P.M. *The Board wishes to announce that it will hold only one Group B, Part I, examination in this and subsequent years.* Candidates who successfully complete the Part I examinations proceed automatically to the Part II examinations held later in the year.

Applications for admission to Group B, Part I, examinations must be on file in the Secretary's office not later than October 4, 1939.

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted by the entire Board, meeting in Atlantic City, N. J., on June 7, 8, and 9, 1940, immediately prior to the annual meeting of the American Medical Association to be held in New York City from June 10 to 14 inclusive.

Applications for admission to Group A, Part II examinations must be on file in the Secretary's office not later than March 15, 1940.

For further information and application blanks, address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

Candidates certified by the American Board of Obstetrics and Gynecology by examination, May, 1939, Meeting at St. Louis, Mo.

GEORGE H. AGNEW, Detroit, Mich.
CARMI R. ALDEN, Boston, Mass.
EDWARD ALLEN, Chicago, Ill.
RUSSELL W. ALLES, Detroit, Mich.
A. N. ARNESON, St. Louis, Mo.
FRANZ ARZT, St. Louis, Mo.
EUGENE S. AUER, Denver, Colo.
MAURICE I. BAKUNIN, Bridgeport, Conn.
ARTHUR BAPTISTI, JR., Baltimore, Md.
LESTER E. BAUER, Detroit, Mich.
CLAYTON T. BEECHAM, Philadelphia, Pa.
SOL J. BENENSOHN, Chicago, Ill.
H. ROBERT BERMAN, Newark, N. J.
EDWARD C. BERNELL, Chicago, Ill.
EDWARD M. BLAIR, Vancouver, Canada
OSCAR H. BLOOM, Brooklyn, N. Y.
THOMAS M. BOULWARE, Birmingham, Ala.
WALLACE B. BRADFORD, Charlotte, N. C.
JOHN I. BREWER, Chicago, Ill.
HAROLD M. BRILL, Chicago, Ill.
JAMES M. BROCKMAN, Memphis, Tenn.
RADFORD BROWN, Washington, D. C.
JOHN A. C. BUSBY, Oak Park, Ill.
ARTHUR C. BUTTS, New York, N. Y.
H. E. CANTER, Pittsburgh, Pa.
GLENN A. CARMICHAEL, Butte, Mont.
EAKLE W. CARTWRIGHT, San Diego, Calif.
JOHN CASAGRANDE, Brooklyn, N. Y.
ALBERT E. CATHERWOOD, Detroit, Mich.
N. EDWARD CLAYMAN, Cleveland, Ohio.
HARRY L. CLARK, Brooklyn, N. Y.
GEORGE G. COCHRAN, JR., Brooklyn, N. Y.
R. M. COLLINS, Council Bluffs, Iowa.
HARRISON S. COLLISI, Grand Rapids, Mich.
JAMES R. COSTELLO, Washington, D. C.
DANA W. COX, Columbus, Ohio.
ROLAND S. CRON, Milwaukee, Wis.
JOSEPH G. CROTTY, Cincinnati, Ohio.
WILLIAM J. CUSACK, Washington, D. C.
HAMPTON P. CUSHMAN, Detroit, Mich.
ALBERT B. DAVIS, Camden, N. J.

M. W. DAVIS, St. Louis, Mo.
JOSEPH DePIETRO, New York, N. Y.
SAMUEL DODEK, Washington, D. C.
EVA F. DODGE, Montgomery, Ala.
WILLIAM A. DWYER, Paterson, N. J.
DOROTHY EDWARDS, Chicago, Ill.
WARD L. EKAS, Rochester, N. Y.
FRANK J. FARA, Cicero, Ill.
GEORGE C. FINOLA, Chicago, Ill.
EDWIN R. FLEMING, Medford, Mass.
PAUL F. FLETCHER, St. Louis, Mo.
CLAIR E. FOLSOME, Ann Arbor, Mich.
OWEN C. FOSTER, Detroit, Mich.
ERNEST W. FRANKLIN, JR., Charlotte, N. C.
FRANK J. FROSCH, Philadelphia, Pa.
HAROLD A. FURLONG, Pontiac, Mich.
R. A. GANDY, Stamford, Conn.
JOHN Z. GASTON, Houston, Texas.
GEORGE O. GAUEN, St. Louis, Mo.
GEORGE B. GERMAN, Camden, N. J.
O. J. GIBSON, St. Louis, Mo.
JAMES L. GILLARD, Muskegon, Mich.
OSCAR GLASSMAN, New York, N. Y.
ASCHER H. C. GOLDFINE, Chicago, Ill.
ROBERT H. GOODWIN, New Bedford, Mass.
GRACE V. GORHAM, Norwalk, Conn.
WILLIAM A. GRAHAM, Durham, N. C.
GEORGE B. GRANGER, Rockville Center, N. Y.
LAMAR A. GRAY, Louisville, Ky.
CRAWFORD GRISWOLD, Bridgeport, Conn.
THOMAS W. GRZEBIEN, Providence, R. I.
JOHN D. GUESS, Greenville, S. C.
WESLEY W. HANFORD, St. Louis, Mo.
GEORGE C. HANNA, JR., Philadelphia, Pa.
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W. O. JOHNSON, Louisville, Ky.
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DWIGHT J. LADD, Chicago, Ill.
ALBERT H. LAHMANN, Milwaukee, Wis.
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PAUL E. LAWLER, Chicago, Ill.
LOYAL E. LEAVENWORTH, Canton, Ohio.
JULIUS G. LEVY, Chicago, Ill.
JAMES P. LEWIS, Philadelphia, Pa.
RICHARD A. LIFVENDAHL, Chicago, Ill.
CHARLES LINTGEN, Philadelphia, Pa.
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G. S. MCCLELLAN, Nashville, Tenn.
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PIERCE MACKENZIE, Evansville, Ind.
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HARRY O. MARYAN, Chicago, Ill.
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EMMETT A. MECHLER, Denver, Colo.
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MILTON H. MEYERHARDT, St. Louis, Mo.
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W. BEDE MITCHELL, Detroit, Mich.
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    Texas.
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JOHN R. WOLFF, Chicago, Ill.
JAMES S. WOLFSTEIN, Cleveland, Ohio.
PAUL W. WOODRUFF, Chicago, Ill.
RAY T. WOOLSEY, Salt Lake City, Utah.
GEORGE J. L. WULFF, JR., St. Louis, Mo.
DWIGHT D. YOUNG, Santa Ana, Calif.

## Biological Photographic Association

The ninth annual Convention will be held September 14 to 16, 1939, at the Mellon Institute for Industrial Research, Pittsburgh, Pa. The program will be of interest to scientific photographers, scientists who use photography as an aid in their work, teachers in the biologic fields, technical experts and serious amateurs. It will include discussions of motion picture and still photography, photomicrography, color and monochrome films, processing, etc., all in the field of scientific illustrating. Up-to-date equipment will be shown in the technical exhibit; and the Print Salon will display the work of many of the leading biologic photographers here and abroad.

Further information about the Association and the Convention may be obtained by writing the Secretary, University Office, Magee Hospital, Pittsburgh, Pa.

## American Congress on Obstetrics and Gynecology

Attention is called again to the meeting to be held in Cleveland, Ohio, on September 11 to 15, 1939.

Complete programs for various sections are now available for distribution. Membership subscriptions now total about 1,500, and it is likely that the attendance will reach several thousands. The success of this undertaking seems assured. A feature will be made of the scientific, educational and commercial exhibits.

For further information address the Headquarter's office, 650 Rush Street, Chicago, Ill.